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Alternative administration of camptothecin analogues

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In order to improve the therapeutic index of camptothecin (CPT) analogues, alternative administration of CPT analogues is being evaluated. Topotecan, irinotecan, rubitecan, lurtotecan and 9-aminocamptothecin have been administered orally with response rates equivalent to that seen after intravenous administration, where applicable. Oral availability and administration of some of the newer CPT analogues, including diflomotecan (BN80915) and grimatecan (ST1481), have also shown promising results. Aerosolisation of liposomal 9-nitrocamptothecin has been studied in patients with advanced malignancies involving the lung, demonstrating systemic antitumour activity. Intrathecal administration of topotecan has been studied in children with refractory neoplastic meningitis. It is well tolerated and associated with some antitumour activity. Intraperitoneal administration of topotecan as consolidation therapy in patients with ovarian cancer has shown promising results. Transdermal administration of rubitecan has been studied in mice. So far, no CPT has been approved for an alternative route of administration.

Keywords: aerosol, camptothecin, chemotherapy, leptomeningeal carcinomatosis, peritoneal carcinomatosis, route of administration, transdermal system

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1. Introduction

Camptothecin (CPT) and its analogues target the topoisomerase-I enzyme (topo-I). Topo-I relaxes DNA by cleaving a single strand of a duplex DNA and allowing passage of the other strand through the nick before religation. Unwinding of the DNA is a prerequisite for processing the genetic information. CPT stabilises the normally transient covalent linkage, also called cleavable complex, between the topo-I and the DNA strand. As malignant cells often contain greater amounts of topo-I than normal cells, they are usually more sensitive to the toxic effects of CPT [1,2]. The alkaloid CPT is the parent compound of topotecan (Hycamtin®, GlaxoSmithKline), irinotecan (Camptosar®, Pfizer), exatecan (DX8951), lurtotecan (GI147211), rubitecan (9-nitrocamptothecin [9NC], RFS2000, Orethecin® [SuperGen]), 9-aminocamptothecin (9AC), karenitecan and other analogues [3,4]. The first four compounds are water-soluble derivatives of CPT, whereas the others are water-insoluble [3,5,6]. Topotecan and irinotecan are commercially available. Exatecan, rubitecan, 9AC, lurtotecan and gimatecan are currently in Phase II and III studies. Other analogues and formulations are either in the preclinical stage or in Phase I studies [3,7-11].

CPT and analogues are in a pH-dependent equilibrium between a closed lactone E-ring and an open carboxylate form. The lactone ring is the active compound required for binding with the topo-I–DNA complex [12-16]. However, at physiological pH in human serum, most of the CPT is in carboxylate form [17]. In human serum, the area under the curve (AUC) of the lactone form is 0 – 30% of the AUC of both forms combined. This observation may be the reason for the low therapeutic index observed with these compounds in humans [18]. The preponderance of preclinical and clinical data indicates that cytotoxic activity of CPT resides in the E-ring lactone [19]. However, correlations between the degree of neutropenia and plasma

Table 1. Summary of camptothecin analogue clinical trials.

Delivery	Topotecan	Irinotecan	Rubitecan	Diflomotecan	Gimatecan	Lurtotecan	9AC
			Tumour type and references				
Oral	Ovarian [32-34] SCLC [35], NSCLC [36] Paediatric solid tumours [37] Glioma [38] Neurobalstoma [39] Leukaemias [40]	Solid tumours [45,46]	Solid tumours [48] Ovarian cancer [49] Pancreatic cancer [50-52] Many other cancer types [53]	Solid tumours [59]	Solid tumours [61,62] Glioma [63,64] Colorectal [65]	Solid tumours [58]	Solid tumours [55-57]
Aerosol			Advanced pulmonary malignancy [74,75]				
Intrathecal	Neoplastic meningitis [84]						
Intraperitoneal	Solid tumours [86] Ovarian [87,88]	Murine models [90-92] Gastric and colon [92]					Peritoneal metastases [89]
Transdermal			Murine models: see Section 5				

9AC: 9-Aminocamptothecin; NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer.

concentrations of lactone and open-ring forms have suggested that the open-ring carboxylate may contribute to myelosuppression [20].

By comparison with other cytotoxic drugs, CPT analogues are ≥ 100-times more potent [2]. The question with CPT analogues is whether these drugs have the capacity to cure the affected animals when tested against human tumours in nude mice models? Once tumours have been eradicated, they usually do not recur. In mice, 50% of the drug present in serum is in the lactone form versus only ~ 10% in the human serum. In humans, the therapeutic index falls dramatically and anticancer responses are observed in < 20% of patients. There is also a considerable percentage of stable disease that usually lasts for 6 months. In fact, with the amount of lactone that reaches the tumour in humans, it is surprising that any responses are observed. The clinical activity of topotecan and other new analogues is most likely to be related to the higher concentration of lactone observed at physiological pH (~ 30% for topotecan), but is compounded by the rapid elimination from the plasma [21,22].

This paper will review novel routes of CPT administration that have been tested clinically and preclinically (see **Table 1** for summary of trials with each administration route). The primary goals of these novel administration routes include optimising the bioavailability, percentage of drug in lactone form, local concentration, and duration of exposure, and reducing the severity and frequency of side effects.

2. Oral administration of camptothecins

Initial interest in the oral administration of CPTs stemmed from data indicating that prolonged exposure to the drugs resulted in greater antitumour activity [23]. Interest was also generated by evidence that patients prefer oral dosing in an out-patient setting to the discomfort and inconvenience of intravenous administration [24]. In addition, oral administration may decrease the administrative costs and the morbidity associated with intravenous dosing (i.e., infection, thrombosis, extravasation) [25]. However, oral administration may result in inadequate absorption, first-pass elimination and variability in plasma levels secondary to individual differences in absorption and metabolism, increasing the risk of both under- and overdosing [26]. Oral administration has been studied for topotecan, rubitecan, 9AC, irinotecan, lurtotecan, gimatecan and diflomotecan.

Topotecan is a water-soluble synthetic CPT, which is approved for use as a second-line therapy in ovarian cancer. At pH 6, > 80% of the total topotecan is in the lactone form, but at physiological pH in the presence of human albumin, topotecan is rapidly hydrolysed to the carboxylate form [27]. A progressive loss of the lactone form in plasma is observed from the start of topotecan infusion. Studies using human tumour xenografts have indicated that oral topotecan was at least as active as with intravenous administration [28]. The oral bioavailability of topotecan is ~ 30 – 40% [29-31]. Coadministration of oral GF120918, a P-glycoprotein and

breast cancer resistance protein inhibitor, in combination with topotecan has been shown to increase the systemic exposure of oral topotecan, increasing the apparent bioavailability from 40 to 97% [30]. A recent population analysis of oral topotecan administration demonstrated that interindividual variability in bioavailability was 22% and that interpatient variability was 22 – 28% [31]. In this study, Cockcroft–Gault creatinine clearance and World Health Organization performance status were significantly correlated to clearance of the drug. The authors recommended consideration of these factors in combination with a limited sampling strategy to monitor the drug and allow for individualised dosing adjustment. Such a strategy may help to reduce dosing concerns about oral CPT administration.

Several studies have compared the oral and intravenous administration of topotecan in ovarian epithelial cancer. A Phase I study in 29 patients with solid tumours showed that with a dosing schedule of oral topotecan for 5 consecutive days every 21 days, the recommended Phase II dose was 2.3 mg/m^2/day, or a fixed dose of 4 mg/day and the dose-limiting toxicity (DLT) was grade IV granulocytopenia [32]. A subsequent Phase II trial in patients with advanced ovarian cancer needing second-line chemotherapy demonstrated that with the schedule described above at 2.3 mg/m^2/day, the response rate was 22%, with similar toxic effects to those described in the Phase I study of oral administration and with intravenous administration [33]. A multicentre, randomised trial designed to compare efficacy, safety and tolerability of oral topotecan compared with the standard intravenous regimen in 266 patients with relapsed ovarian cancer found that response rates were 13% orally and 20% intravenously, although this difference was not statistically significant [34]. There was a small but statistically significant difference in median survival between the two groups (51 weeks in the oral arm and 58 weeks in the intravenous arm, $p = 0.033$). In addition, the study found that the principal toxicity, grade IV neutropenia, occurred less frequently in those receiving oral topotecan (15 versus 51% of cycles). The decrease in myelosuppression may be due to the lower maximum concentration (C_{max}) and AUC for oral topotecan.

Oral topotecan had also been studied in small-cell lung cancer (SCLC). A Phase II study of patients with relapsing chemosensitive SCLC found that those receiving 2.3 mg/m^2/day x 5 every 21 days had a response rate of 23% compared with 15% in the intravenous arm [35]. Grade IV neutropenia occurred in 35% of patients on oral topotecan and in 67% of patients with intravenous administration ($p = 0.001$). A similar Phase III trial is underway. Oral topotecan has also shown modest activity in the treatment of non-small-cell lung cancer (NSCLC) [36].

Several studies of oral topotecan in paediatric tumours have recently been performed. A Phase I study in paediatric patients with refractory solid tumours showed that the maximum tolerated dose (MTD) for oral topotecan was 1.8 mg/m^2/day for 5 days for 2 consecutive weeks, with myelosuppression and diarrhoea as the dose-limiting effects [37]. Recent Phase I and II trials of oral topotecan have shown good tolerance and efficacy in children with progressive high-grade glioma [38]. A recent retrospective analysis found that oral topotecan had antitumour activity in a small percentage of patients with relapsed or refractory neuroblastoma [39].

Oral topotecan has also been studied in a Phase I trial in haematological malignancies (myelodysplastic syndromes, myeloproliferative disorders and relapsed acute myelogenous leukaemia) [40]. DLTs included grade III or IV nausea/vomiting at 1.9 mg/m^2/day. Haematological-toxicity was also noted, but was not considered dose limiting. A total of 17% of patients achieved complete response, whereas 25% experienced haematological improvement, thus warranting further investigation.

Oral administration of the water-soluble CPT analogue irinotecan has also been investigated. Irinotecan is a water-soluble synthetic CPT first approved in the US for treatment of advanced colorectal cancer refractory to fluorouracil. The major active metabolite of irinotecan is SN-38 (7-ethyl-10-hydroxycamptothecin) [41]. A carboxylesterase catalyses the conversion of irinotecan to SN-38 [42,43]. Carboxylesterase activity is usually higher in tumour cells, including lymphoma, SCLC, endometrial cancer and mesothelioma. The carboxylesterase activity correlates with the antitumour activity [42]. *In vitro* studies have indicated that SN-38 has 100- to 1000-fold greater antitumour activity than irinotecan itself. SN-38 is inactivated by glucuronidation [44].

Phase I studies of oral administration demonstrated that the MTD for oral irinotecan was 66 mg/m^2/day in patients < 65 years of age and 50 mg/m^2/day in patients aged ≥ 65 years, administered daily for 5 days every 3 weeks [45]. The DLT was diarrhoea, similar to that observed with intravenous administration of the drug. Bioavailability of the drug after oral administration is low (8%) [46]. Therefore, few Phase II trials have investigated oral irinotecan and the drug is currently administered predominantly intravenously.

Oral administration of rubitecan, a water-insoluble CPT with broad antitumour activity in animal models, has been studied extensively. A sampling schedule allowing assessment of the pharmacokinetic parameters of both 9NC and its metabolite 9AC after oral administration has been described [47]. Phase I studies in patients with refractory advanced cancer estimated the MTD to be 1.5 mg/m^2/day for 5 consecutive days every week [48]. DLT was haematological, but significant gastrointestinal and urinary bladder toxicity was also noted. Pharmacokinetic analysis revealed that the mean AUC of lactone versus total drug was 14.7% (standard deviation [SD] ± 13.4). Phase II trials of oral 9NC have been performed for a wide range of cancers. In patients with refractory ovarian cancer, 1.5 mg/m^2/day for 4 consecutive days every week was administered with increments of 0.25 mg/day for patients without significant side effects [49]. The lactone concentration was substantially lower than the total drug concentration in the plasma (0 – 20% of total drug concentration). A 7% remission rate was observed and 34% of patients had

stable disease. Median survival was 8 months. Haematological toxicity was most prominent. Oral 9NC in pancreatic cancer has also shown promising results. A Phase II study in patients with advanced pancreatic cancer demonstrated that oral 9NC at 1.5 mg/m^2/day for 5 days/week for ≥ 8 weeks resulted in response rates of 32% in evaluated patients [50]. DLT was myelosuppression and interstitial cystitis. A second Phase II study in patients with advanced pancreatic cancer demonstrated similar results, with a 29% objective response to oral rubitecan in assessable patients [51]. However, a third Phase II trial using more stringent criteria for response found a response rate of only 9% in patients with previously treated pancreatic cancer [52].

Phase II studies of oral 9NC at similar dosing schedules to those described above have demonstrated little antitumour activity in breast cancer, colon cancer, advanced/metastatic urothelial tract tumours, glioblastoma multiform, melanoma, soft tissue sarcoma, NSCLC and SCLC (see Hewes *et al.* for a recent review [53]). 9NC continues to be studied in combination with numerous other chemotherapeutic agents.

9AC, a metabolite of 9NC, is a poorly water-soluble CPT, which has been studied in several different formulations to increase absorption. Durations of exposure are believed to be essential, stimulating interest in oral dosing [23]. One such formulation is 9AC polyethylene glycol (PEG)-1000 capsules [54]. In a Phase I study of 30 patients with solid tumours, administered 9AC PEG-1000 capsules 0.25 – 1.1 mg/m^2/day x 7 – 14 days every 21 days p.o., the DLT was myelosuppression and diarrhoea at 1.1 mg/m^2/day x 14 day [55]. One partial response was noted. The majority of the drug absorbed was converted from the lactone form, with $9AC_{carboxylate}$ accounting for 90.9 ± 3.32% of the total drug. Although intrapatient variability was small, interpatient variability was quite large. The AUC of $9AC_{lactone}$ was significantly correlated with the decrease in white blood cells ($p < 0.001$). Recommended Phase II dosing was 0.84 mg/m^2/day x 14 days, a dose that achieved the threshold concentration for antitumour effect for several hours on each day of treatment. However, given the interpatient variability, the authors recommended further pharmokinetically guided Phase II studies. 9AC has also been administered orally as a colloidal dispersion (9ACCD). In 32 patients with solid tumours, patients received one intravenous dose of 9ACCD and then 0.2 – 0.7 mg/m^2/day p.o. x 4 weeks followed by 2 week's rest [56]. DLT was myelosuppression at 0.7 mg/m^2/day. There was no objective response. Mean total bioavailability was 68.1 ± 36.4%. Mean half-lifes of $9AC_{lactone}$ and $9AC_{total}$ were 6.9 ± 3.2 and 1.2 ± 1.2 h, respectively. As in the above study of 9AC PEG-1000, there was high interpatient variability in AUC and bioavailability. This study confirmed the results of an earlier Phase I trial of 9ACCD [57]. The above trials indicate that oral 9AC may not be suitable for further clinical development.

Lurtotecan is a water-soluble CPT analogue, which has been administered orally. In 19 patients with refractory solid tumours treated with 1.5 – 6 mg/m^2 x 5 days every 3 weeks, neutropenia and thrombocytopenia were the major side effects [58]. At 6 mg/m^2, T_{max} (time to C_{max}) was 0.63 ± 0.4 h. C_{max} was 4.02 ± 3.57 ng/ml compared with 21.76 ± 6.37 ng/ml with intravenous administration. Absolute bioavailability of the lactone form of oral lurtotecan was 11.3 ± 5.2%, which was close to the bioavailability of total lurtotecan at 11.8 ± 4.5%. There was wide interpatient variation in bioavailability. Mean terminal half-life was 6.8 ± 3.1 h, again similar to intravenous administration. Short-lasting stable disease was observed in seven patients. The authors recommended intravenous administration in future studies given the wide interpatient variability. Current research is focused on intravenous administration of liposomal formulations of lurtotecan.

Oral availability and administration of some of the newer CPT analogues has been studied. Diflomotecan is an E-ring modified CPT analogue thought to have greater lactone stability. In a Phase I trial of oral diflomotecan in adult patients with solid malignant tumours the mean oral bioavailability was high but variable (72.24 ± 59.2% across all dose levels) [59]. The recommended oral diflomotecan dose for Phase II studies was a flat dose of 0.27 mg/day x 5 every 3 weeks. The main toxicity was haematological.

Gimatecan is a lipophilic CPT derivative designed for oral administration, which has shown antitumour activity against a large panel of human tumour xenografts [60]. Several Phase I trials address dosing and safety of oral administration. In one study, 12 patients have been evaluated at doses in the range of 0.26 – 1.32 mg/m^2/week [61]. The drug is rapidly absorbed and slowly eliminated with a mean apparent half-life of 108 ± 40 h. The compound exists in the plasma almost entirely as the active, intact lactone species. The authors concluded that oral administration once a week provides continuous exposure to potentially effective plasma concentrations of the drug. A second Phase I trial tested three schedules and recommended Phase II dosing at 4 – 4.5 mg/m^2/cycle everyday for 5 days in a 28-day schedule and 5 – 5.6 mg/m^2/cycle with 5 days on/2 days off on weeks 1 and every 2 days in a 28-day schedule [62]. As in the previous trial, the half-life was long (83 h). DLT was haematological. Two Phase I trials in patients with malignant gliomas showed enhanced clearance of gimatecan by enzyme-inducing antiepileptic drugs [63,64]. The drug was well tolerated in these trials and showed initial promising results. A Phase II study has demonstrated tolerability and activity in metastatic colorectal carcinoma with the 5 and 5.6 mg/m^2/cycle schedule described above [65]. Haematological toxicity was noted as the 5.6 mg/m^2/cycle dose, but was acceptable with dose reduction to 5 mg/m^2/cycle. The study is ongoing.

3. Aerosolised administration of liposomal rubitecan

Previous works have shown that certain drugs delivered to the respiratory tract in a liposome formulation may have advantages including high pulmonary concentrations, often rapid entry into the systemic circulation, reduced toxicity and reduced dosage requirement compared with

oral and parenteral administration [42,43]. Dilauroylphosphatidylcholine (DLPC) aerosol formulations of beclomethasone and cyclosporin have already been administered in the clinical setting [66-69].

Pharmacokinetic studies of liposome aerosols in mice with CPT showed high concentrations of CPT in the lungs with rapid diffusion to the liver, tumour, brain and other organs [70]. In a nude mouse model, 9NC-DLPC liposome aerosol has demonstrated a favourable therapeutic index (with significantly reduced tumour growth rate and tumour shrinkage) without serious side effects in three different human cancer xenografts: breast, colon and lung [71]. The liposome formulation may help to keep the E-ring closed for penetration in tumour cells. In animal models, equivalent activity of liposomal 9NC, as compared with the nonliposomated drug, is seen at a fifth or less of the dose. Toxicity profiles in the mouse indicate a MTD of ~ 4 mg/kg when given orally; however, the maximum aerosol dose tested so far, of 307 µg/kg/day, was nontoxic. Such activity was noted in the absence of weight loss or other evident side effects [72]. 9NC–DLPC liposomes have been shown to be nontoxic to dogs when given for 5 days/week for 8 weeks [73].

Aerosolised liposomal 9NC–DLPC has been studied in a Phase I trial in patients with advanced pulmonary malignancies [74,75]. Patients were eligible if they had primary or metastatic cancer in the lungs, failed standard chemotherapy regimens for their disease, normal bone marrow function and normal hepatic and renal functions, no known respiratory disease other than cancer, and acceptable pulmonary function defined as forced expiratory volume for 1 s (FEV_1), FEV_1/force vital capacity, total lung capacity, and diffusion capacity of carbon monoxide all > 50% of predicted values. Treatment in the feasibility cohort consisted of 9NC 6.7 µg/kg/day in aerosol reservoir for 60 min/day for 5 consecutive days/week for 1, 2, 4 or 6 weeks, then observation for 2 weeks. For the Phase I part of the study, doses were increased stepwise from 6.7 to 26.6 µg/kg/day for 5 consecutive days for 8 weeks followed by 2 week's rest. A total of 25 patients received treatment. DLT was chemical pharyngitis seen in two of the patients at 26.6 µg/kg/day. At 20 µg/kg/day grade II and III fatigue required dose reduction in two of four patients. A reversible decrease in FEV_1 was also noted in patients treated with the aerosolised drug. Interestingly, there was no significant haematological toxicity, although 9NC plasma levels were similar to those observed after oral ingestion. The recommended dose for Phase II studies was 13.3 µg/kg/day delivered as two consecutive 30 min nebulisations/day from a nebuliser reservoir with 9NC 4 mg in 10 ml water, for 5 consecutive days for 8 weeks every 10 weeks. Partial remissions were observed in two patients with uterine cancer and stabilisation occurred in three patients with primary lung cancer. A partial remission of a liver metastasis was also observed in a patient with endometrial cancer, thus demonstrating the systemic potential of aerosol delivery. Pharmacokinetic studies demonstrated that total 9NC plasma concentration continued to increase for 2 – 3 h from the start of treatment reaching a mean (± SD) peak concentration of 37.7 ± 20.2 ng/ml at 2 h. Mean (± SD) clearance was biphasic with a half-life-α of 1.9 ± 1.4 h and a half-life-β of 16.4 ± 10.5 h. The AUC of the lactone form measured in two patients comprised 3.2 and 3.5% of the total 9NC. 9NC concentrations in bronchoalveolar lavage fluid were 4.2- to 10.6-times higher than those measured concurrently in plasma.

Several recent animal studies have looked at aerosol delivery of 9NC in combination with other chemotherapeutic agents. A recent study in mice examined the anticancer properties of an acetic acid analogue of vitamin E, 2,5,7,8-tetramethyl-2*R*-(4*R*,8*R*,12-trimethyltridecyl)chroman-6-yloxyacetic acid (α-TEA), and 9NC against mouse mammary tumour cells [76]. Combination treatment enhanced antiproliferative and pro-apoptotic activities both in cell culture and when formulated in liposomes by means of aerosolisation to treat metastatic murine mammary tumour. Of interest, the combination treatment showed a significant reduction in tumour volume in comparison with either treatment alone. A second study examined the growth inhibition of B16-F10 melanoma lung metastases in mice by sequential aerosol delivery of polyethyleneimine-p53 DNA (PEI-p53) and 9NC-DLPC [77]. Sequential delivery of both agents acted additively to inhibit the growth of established tumour metastases and lead to a 30 – 40% increase in mean survival time in treated mice.

4. Intrathecal administration of camptothecins

Neoplastic meningitis remains a significant diagnostic and treatment challenge for clinical oncologists, and the long-term outcome for most patients with leptomeningeal metastases from an underlying solid tumour or recurrent leptomeningeal leukaemia or lymphoma is poor. Systemic chemotherapy may be helpful in specific conditions such as gestational trophoblastic disease to eradicate brain disease, but is usually of little help because the penetration of most drugs into the cerebrospinal fluid (CSF) is limited by the blood–brain barrier. This may not be true for topotecan. Following systemic administration of 10 mg/m^2 i.v. over 10 min in a nonhuman primate model, topotecan penetrated the CSF and lactone concentration reached 30% [78]. Direct intrathecal instillation of anticancer drugs is another approach, which has been used to circumvent the pharmacological sanctuary imposed by the blood–brain barrier. As few anticancer agents can safely be administered by the intrathecal route, the effectiveness of this form of regional therapy is limited. In recent years the development of several promising new intrathecal agents (e.g., diaziquone, mafosfamide and DTC101) [79-81] has been possible through the use of a unique nonhuman primate model [82]. Intrathecal topotecan has successfully been tested in this model. Pharmacokinetic studies performed following a direct intraventricular dose of 0.1 mg demonstrated that a 450-fold greater CSF exposure could be achieved with one-hundreth

the systemic dose [83]. No systemic or neurotoxicity, with the exception of a transient pleocytosis in 30% of animals, was observed following intraventricular topotecan administration. Further studies to evaluate the long-term toxicity of weekly intralumbar injections of topotecan were performed in three animals that received topotecan 0.1 mg by means of lumbar puncture weekly for 4 weeks. This dose was well tolerated, without evidence of myelosuppression, neurotoxicity or pleocytosis. These preclinical studies served as the basis for a Phase I study of intrathecal topotecan in patients with refractory neoplastic meningitis [84].

Intrathecal topotecan was administered twice weekly during a 4 – 6 week induction, followed by a consolidation phase of 4 weekly doses, then a twice-monthly maintenance phase for 4 months, and monthly thereafter for up to 8 additional months. Patients with disease progression at any time during the study were removed. The starting dose was 0.025 mg. In the first cohort of patients, weekly intrapatient dose escalations to 0.05, 0.1 and 0.2 mg were carried out. Subsequent cohorts were treated without escalation at 0.2, 0.4 or 0.7 mg. A total of 29 patients enrolled in the study and 23 patients were assessable for toxicity and response. The median age was 12 years (range 3 – 63 years). Tumours included medulloblastoma/primitive neuroectodermal tumour (nine patients), gliomatosis [2], ependymoma [1], pineoblastoma [1], acute lymphoblastic leukaemia [3], retinoblastoma [3], breast cancer [2] and lung cancer [2]. Chemical arachnoiditis was the DLT in two of the four patients and a non-DLT in one of the patients at the 0.7-mg dose level. All resolved with cessation of therapy and/or decadron treatment. A transient, mild CSF pleocytosis was observed in two of these patients. Grade III ataxia developed in one patient treated with the 0.4-mg dose and did not completely resolve after discontinuation of topotecan. Non-DLTs included nausea, vomiting, headache and transient leukopenia. Another adverse event consisted of staring with myoclonic jerking after the third dose (n = 1).

Mean (± SD) CSF topotecan levels in patients with indwelling Ommaya reservoirs treated at the MTD (0.4 mg) was 28 ± 11 µmol/l. In CSF the terminal elimination half-life was 157 ± 54 min. The lactone drug clearance was more rapid than total drug clearance, although only two patients were evaluated. Lumbar total drug concentrations were an average of 15 ± 10% of the simultaneously drawn ventricular concentrations. One of the three patients with acute lymphoblastic leukaemia had a complete response to induction therapy. The other two had clearing or marked reduction of CSF cell counts, but were removed from the study to receive other treatments. Three of the patients with primary CNS tumours (medulloblastoma, gliomatosis and glioblastoma multiform) also experienced benefit. In summary, intrathecal administration of topotecan is well tolerated at doses ≤ 0.4 mg and is associated with some antitumour activity. A Phase II study of topotecan in children with neoplastic meningitis is planned.

No other CPTs have been administered intrathecally. However, a plasma and CSF pharmacokinetics study of intravenous 9AC and irinotecan in a nonhuman primate model has been performed [85]. 9AC at two dose levels (4 and 10 mg/m^2) was infused intravenously over 15 min and irinotecan (96 and 225 mg/m^2) was infused over 30 min. Plasma and CSF samples were obtained at frequent intervals over 24 h. Lactone and total drug forms of 9AC, irinotecan and the active metabolite of irinotecan, SN-38, were then quantified. The CSF penetration of 9AC lactone was limited with an area under the CSF concentration curve (AUC_{CSF}):area under the plasma concentration curve (AUC_P) of only 3.5 ± 2.1%. For irinotecan, the AUC_{CSF}:AUC_P ratio for irinotecan lactone was 14 ± 3%. SN-38 lactone could not be measured in CSF. CSF penetration of 9AC and SN-38 is substantially less than that of topotecan, which has an AUC_{CSF}:AUC_P ratio of 32%.

Further study of intrathecal CPT is warranted in an attempt to identify effective new agents that will expand the limited armamentarium of anticancer agents that are available for intrathecal administration.

5. Intraperitoneal administration of camptothecins

Intraperitoneal administration of topoisomerase inhibitors may have pharmacological benefits over intravenous administration, especially for topo-I inhibitor-sensitive malignancies confined to the peritoneal cavity. Persistence of the active lactone form in the peritoneal cavity would be a definite advantage.

Two Phase I studies have been looking at one administration of topotecan (either over 24 or 1 h) every 3 weeks. The maximum tolerated doses were 3 and 20 mg/m^2, respectively. In the first Phase I trial 15% of the total dose was given as an intraperitoneal bolus in 2 litres of 5% dextrose in water and the remainder was given as a continuous intraperitoneal infusion over 24 h [86]. DLT was neutropenia. Other toxicities included leukopenia, anaemia, emesis, fever and abdominal pain. No objective responses were achieved, although 5 of 10 patients with ascites had a decrease in fluid accumulation with administration of intraperitoneal topotecan. Elimination of topotecan from the peritoneal cavity followed second-order kinetics with first- and second-phase half-life of 0.49 and 2.7 h, respectively. Plasma pharmacokinetic fitted first-order kinetics with a half-life of 3.9 h. The area under the peritoneal concentration curve ($AUC_{peritoneal}$):AUC_P ratio was 31.2.

The second study was in patients with advanced recurrent ovarian cancer not previously treated with CPTs [87]. Topotecan was administered intraperitoneally with 1 litre of normal saline (pH = 4) over 1 h. The projected dose steps of topotecan were 5 – 30 mg/m^2/day i.p. in three patients on each dose level. Cycles were repeated every 3 weeks to a maximum of eight. DLT was skin rash and fever with hypotension in one patient at 30 mg/m^2. Thus, MTD was 20 mg/m^2. A second patient had similar symptoms plus grade III – IV haematological toxicity at 15 mg/m^2. However, in general, haematological toxicity was grade II or less. Other toxicities included nausea, vomiting and abdominal pain. The

Table 2. Transdermal administration of CPT and rubitecan in a nude mouse model.

Treatment twice a week	Dose (mg/kg of CPT)	Dose (mg/kg of rubitecan)	Number of animals surviving	Days to maximum tumour inhibition
Controls	0	0	3/27 (rubitecan) 4/20 (CPT)	None
Intragastric	2	2	3/4 (CPT) 2/4 (rubitecan)	30
Transdermal	5 –10	5 – 10	24/24 (rubitecan) 27/33 (CPT)	30 for rubitecan 40 for CPT
Transdermal vaseline carrier		6 and 7.5	11/14	28
Transdermal cotton seed oil carrier		5, 6 and 7.5	14/16	28
Transdermal 20% DMSO carrier		7.5	3/4	28

CPT: Camptothecin; DMSO: Dimethyl sulfoxide.

peritoneal lactone/total topotecan AUC ratio was 15 – 52%, median 29% and the peritoneal to plasma AUC ratio for total topotecan was 54 ± 34. Total topotecan was cleared from the peritoneal cavity with a half-life = 2.7 ± 1.7 h. The plasma AUC ratio of lactone versus total topotecan increased with dose from 16 to 55%. Plasma half-life was 3.7 ± 1.3 h. Pharmacokinetic data were in agreement with the other Phase I study described above [86]. The authors noted that plasma topotecan concentrations required for cytotoxicity *in vitro* were reached from the 15-mg/m^2 dose onward. No complete clinical responses were observed. Partial response, defined as a > 50% decrease in cancer antigen 125 (CA125) levels were observed in 6 of 13 patients. Progressive disease was observed in six patients. The low levels of haematological toxicity observed in this study may allow multiagent therapy with intraperitoneal topotecan and active intravenous doses of other cytotoxic drugs including paclitaxel and platinum compounds while avoiding intolerable haematological side effects [87].

A Phase II study of intraperitoneal topotecan as consolidation therapy in patients with ovarian cancer showed promising results [88]. Patients with stage III/IV ovarian cancer in clinical complete response after surgical cytoreduction and intravenous chemotherapy with negative macroscopic disease at second-look surgery were eligible. Intraperitoneal topotecan 20 mg/m^2 in 1 litre normal saline was infused into the peritoneum once every 21 days for four to six cycles. Major toxicity was haematological. All 10 patients have remained in complete remission for a median of 14 months.

Intraperitoneal administration of 9AC has also been looked at in a Phase I study in patients with minimal disease of the peritoneal cavity [89]. The study employed a dose-escalation design with levels in the range of 1.25 – 13.5 mg/m^2/cycle. Treatment was given over 2 weeks followed by a 2-week rest in a 4-week cycle. The $AUC_{peritoneal}$:AUC_P ratio was in the range of 7.6 – 16.5. Different DLTs were noted in three of four patients at the highest dose (13.5 mg/m^2), including grade 4 haematologic toxicity, elevation of liver function studies and aseptic peritonitis. A dose of 9 mg/m^2 was recommended for Phase II studies. Of the seven evaluable patients, two patients had objective evidence of clinical benefit and one had progressive disease.

Intraperitoneal irinotecan has been studied in mouse models and compared with intravenous and oral administration. Oral administration resulted in greater tumour inhibition than via the intraperitoneal route [90]. In comparison, intravenous administration was worse than intraperitoneal administration both in terms of survival of the animals and pharmacokinetics. Peritoneal clearance of irinotecan was 10-fold lower after intraperitoneal versus intravenous administration, resulting in a longer exposure to irinotecan after intraperitoneal administration [91]. A second animal study demonstrated that intraperitoneal administration of irinotecan was more effective than intravenous administration of irinotecan for both peritoneal seeding and liver metastases [92]. In four human patients with peritoneal seeding of gastric and colonic cancer, intraperitoneal irinotecan was effective for the control of malignant ascites [92]. However, the active SN-38 form of the drug was present in equal levels in plasma and peritoneal fluid, implying that there may be no direct biotransformation of irinotecan to SN-38 by cancer cells on the peritoneal surface, making this route of administration no more beneficial.

Interestingly, intraperitoneal 20(*s*)-CPT has been shown to significantly reduce parasite load in a murine model of visceral leishmaniasis, with efficient delivery of the drug to both the liver and spleen [93].

6. Transdermal and intramuscular administration of camptothecins

Transdermal administration has been tested in nude mice bearing different human tumours. The drugs tested were CPT and 9NC. Drugs were formulated in patches, or used with a liposoluble vehicle. The vehicles used were vaseline, cotton-seed oil

or 20% dimethyl sulphoxide. A human topo-I inhibitor-sensitive breast cancer was extensively tested (**Table 2**). Results show that transdermal administration is as good as oral administration. Patches were selected for further studies. Other human tumours tested with 9NC patches included colon, melanoma and lung. Patches of 9NC were applied twice a week on the skin until the tumours disappeared. The dose of 9NC for the patches was 7.5 mg/kg twice a week. Antitumour activity was comparable to oral doses (through direct intragastric injections) of 9NC 1.5 mg/kg for 3 days every 4 days.

Weekly intramuscular injections were tested at low doses of 9NC (0.75 – 1 mg/kg) either as a liposome or mixed with cotton seed oil. The best tumour inhibition was seen with 9NC in cotton seed oil.

7. Expert opinion

CPTs are drugs that are well suited for various modes of administration. In animal models, longer exposures seem to produce more antitumour activity. The CPTs are absorbed systemically through the gastrointestinal tract, the lungs and the skin. When administered through the peritoneal cavity or the intrathecal space, systemic absorption is present, but reduced, leaving high concentration of drugs in these bodily cavities.

The main problem that remains to be solved is the equilibrium of the lactone versus the carboxylate forms, which in humans favours the inactive (carboxylate) form. Until now, alternative administrations of CPT have not been shown to significantly help shift the equilibrium to the lactone form. However, activity is seen and may be similar to that observed after intravenous administration. No CPT has yet been approved for an alternative route of administration. In the future, new delivery systems such as liposomes, polyethylene glycol esters or polymers, as well as new derivatives, need to be studied in an attempt to stabilise the lactone form.

The main future for CPTs will probably be the further development of intrathecal and aerosol delivery, as CPTs are very well tolerated when administered in these ways. Further studies of intraperitoneal administration may benefit from a change in formulation and pH to improve the lactone/carboxylate equilibrium and retention in this body cavity.

Bibliography

1. LIEBES L, POTMESIL M, KIM T *et al.*: Pharmacodynamics of topoisomerase I inhibition: western blot determination of topoisomerase I and cleavable complex in patients with upper gastrointestinal malignancies treated with topotecan. *Clin. Cancer Res.* (1998) 4:545-557.
2. GIOVANELLA BC, STEHLIN JS, WALL ME *et al.*: DNA topoisomerase I - targeted chemotherapy of human colon cancer in xenografts. *Science* (1989) **246**:1046-1048.
3. GARCIA-CARBONERO R, SUPKO JG: Current perspectives on the clinical experience, pharmacology, and continued development of the camptothecins. *Clin. Cancer Res.* (2002) **8**:641-661.
4. PIZZOLATO JF, SALTZ LB: The camptothecins. *Lancet* (2003) **361**:2235-2242.
5. VERSCHRAEGEN C, KUDELKA AP, KAVANAGH JJ: Topoisomerase-I inhibitors in gynecologic tumors. *Ann. Acad. Med. Singapore* (1998) **27**:683-687.
6. BALAT O, VERSCHRAEGEN C: Topoisomerase I inhibitors in gynecologic cancers. *Expert Opin. Investig. Drugs* (1995) **4**:1217.
7. HALUSKA P, RUBIN E, VERSCHRAEGEN C: Topoisomerase-I inhibitors in gynecologic tumors. *Hematol. Oncol. Clin. North Am.* (1999) **13**:43-61.
8. STEVENSON JP, DE MARIA D, SLUDDEN J *et al.*: Phase I pharmacokinetic study of the topoisomerase I inhibitor GG211 administered as a 21-day continuous infusion. *Ann. Oncol.* (1999) **10**:339-344.
9. SCHOEMAKER NE, VAN KESTEREN C, ROSING H *et al.*: A Phase I and pharmacokinetic study of MAG-CPT, a water-soluble polymer conjugate of camptothecin. *Br. J. Cancer* (2002) **87**:608-614.
10. BISSETT D, CASSIDY J, DE BONO JS *et al.*: Phase I and pharmacokinetic (PK) study of MAG-CPT (PNU 166148): a polymeric derivative of camptothecin (CPT). *Br. J. Cancer* (2004) **91**:50-55.
11. GILES FJ, TALLMAN MS, GARCIA-MANERO G *et al.*: Phase I and pharmacokinetic study of a low-clearance, unilamellar liposomal formulation of lurtotecan, a topoisomerase 1 inhibitor, in patients with advanced leukemia. *Cancer* (2004) **100**:1449-1458.
12. JAXEL C, KOHN KW, WANI MC, WALL ME, POMMIER Y: Structure–activity study of the actions of camptothecin derivatives on mammalian topoisomerase I: evidence for a specific receptor site and a relation to antitumor activity. *Cancer Res.* (1989) **49**:1465-1469.
13. NABIEV I, FLEURY F, KUDELINA I *et al.*: Spectroscopic and biochemical characterization of self-aggregates formed by antitumor drugs of the camptothecin family: their possible role in the unique mode of drug action. *Biochem. Pharmacol.* (1998) **55**:1163-1174.
14. CHOURPA I, RIOU JF, MILLOT JM, POMMIER Y, MANFAIT M: Modulation in kinetics of lactone ring hydrolysis of camptothecins upon interaction with topoisomerase I cleavage sites on DNA. *Biochemistry* (1998) **37**:7284-7291.
15. CARRIGAN SW, FOX PC, WALL ME, WANI MC, BOWEN JP: Comparative molecular field analysis and molecular modeling studies of 20-(*S*)-camptothecin analogs as inhibitors of DNA topoisomerase I and anticancer /antitumor agents. *J.Comput. Aided Mol. Des.* (1997) **11**:71-78.
16. RIVORY LP, ROBERT J: Molecular, cellular, and clinical aspects of the pharmacology of 20(*S*)camptothecin and its derivatives. *Pharmacol. Ther.* (1995) **68**:269-296.
17. GABR A, KUIN A, AALDERS M, EL-GAWLY H, SMETS LA: Cellular pharmacokinetics and cytotoxicity of camptothecin and topotecan at normal and acidic pH. *Cancer Res.* (1997) **57**:4811-4816.
18. VERSCHRAEGEN CF, NATELSON EA, GIOVANELLA BC *et al.*: A Phase I clinical and pharmacological study of oral 9-nitrocamptothecin, a novel water-insoluble topoisomerase I inhibitor. *Anti-Cancer Drugs* (1998) **9**:36-44.

19. HERTZBERG RP, CARANFA MJ, HOLDEN KG *et al.*: Modification of the hydroxy lactone ring of camptothecin: inhibition of mammalian topoisomerase I and biological activity. *J. Med. Chem* (1989) **32**:715-720.
20. MOERTEL C, SCHUTT A, REITEMEIER R, HAHN R: Phase II study of camptothecin in the treatment of advanced gastrointestinal cancer. *Cancer Chemother. Rep.* (1972) **56**:95-101.
21. HERBEN VM, TEN BOKKEL HUININK WW, BEIJNEN JH: Clinical pharmacokinetics of topotecan. *Clin. Pharmacokinet.* (1996) **31**:85-102.
22. VAN WARMERDAM LJ, CREEMERS GJ, RODENHUIS S *et al.*: Pharmacokinetics and pharmacodynamics of topotecan given on a daily-times-five schedule in Phase II clinical trials using a limited-sampling procedure. *Cancer Chemother. Pharmacol.* (1996) **38**:254-260.
23. GERRITS CJ, DE JONGE MJ, SCHELLENS JH, STOTER G, VERWEIJ J: Topoisomerase I inhibitors: the relevance of prolonged exposure for present clinical development. *Br. J. Cancer* (1997) **76**:952-962.
24. LIU G, FRANSSEN E, FITCH MI, WARNER E: Patient preferences for oral versus intravenous palliative chemotherapy. *J. Clin. Oncol.* (1997) **15**:110-115.
25. SPARREBOOM A, DE JONGE MJ, VERWEIJ J: The use of oral cytotoxic and cytostatic drugs in cancer treatment. *Eur. J. Cancer* (2002) **38**:18-22.
26. HUDES G: Boosting bioavailability of topotecan: what do we gain? *J. Clin. Oncol.* (2002) **20**:2918-2919.
27. DENNIS MJ, BEIJNEN JH, GROCHOW LB, VAN WARMERDAM LJ: An overview of the clinical pharmacology of topotecan. *Semin. Oncol.* (1997) **24**:S512-S518.
28. PRATESI G, DE CESARE M, ZUNINO F: Improvement of therapeutic index of low-dose topotecan delivered *per os*. *Ann. NY Acad. Sci.* (2000) **922**:330-333.
29. SCHELLENS JH, CREEMERS GJ, BEIJNEN JH *et al.*: Bioavailability and pharmacokinetics of oral topotecan: a new topoisomerase I inhibitor. *Br. J. Cancer* (1996) **73**:1268-1271.
30. KRUIJTZER CM, BEIJNEN JH, ROSING H *et al.*: Increased oral bioavailability of topotecan in combination with the breast cancer resistance protein and P-glycoprotein inhibitor GF120918. *J. Clin. Oncol.* (2002) **20**:2943-2950.
31. LEGER F, LOOS WJ, FOURCADE J *et al.*: Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. *Br. J. Cancer* (2004) **90**:343-347.
32. GERRITS CJ, BURRIS H, SCHELLENS JH *et al.*: Five days of oral topotecan (Hycamtin), a Phase I and pharmacological study in adult patients with solid tumours. *Eur. J. Cancer* (1998) **34**:1030-1035.
33. CLARKE-PEARSON DL, VAN LE L, IVESON T *et al.*: Oral topotecan as single-agent second-line chemotherapy in patients with advanced ovarian cancer. *J. Clin. Oncol.* (2001) **19**:3967-3975.
34. GORE M, OZA A, RUSTIN G *et al.*: A randomized trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer. *Eur. J. Cancer* (2002) **38**:57-63.
35. VON PAWEL J, GATZEMEIER U, PUJOL JL *et al.*: Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. *J. Clin. Oncol.* (2001) **19**:1743-1749.
36. WHITE SC, CHEESEMAN S, THATCHER N *et al.*: Phase II study of oral topotecan in advanced non-small cell lung cancer. *Clin. Cancer Res.* (2000) **6**:868-873.
37. DAW NC, SANTANA VM, IACONO LC *et al.*: Phase I and pharmacokinetic study of topotecan administered orally once daily for 5 days for 2 consecutive weeks to pediatric patients with refractory solid tumors. *J. Clin. Oncol.* (2004) **22**:829-837.
38. WAGNER S, ERDLENBRUCH B, LANGLER A *et al.*: Oral topotecan in children with recurrent or progressive high-grade glioma: a Phase I/II study by the German Society for Pediatric Oncology and Hematology. *Cancer* (2004) **100**:1750-1757.
39. KRAMER K, KUSHNER BH, CHEUNG NK. Oral topotecan for refractory and relapsed neuroblastoma: a retrospective analysis. *J. Pediatr. Hematol. Oncol.* (2003) **25**:601-605.
40. BERAN M, O'BRIEN S, THOMAS DA *et al.*: Phase I study of oral topotecan in hematological malignancies. *Clin. Cancer Res.* (2003) **9**:4084-4091.
41. KAWATO Y, AONUMA M, HIROTA Y, KUGA H, SATO K: Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Res.* (1991) **51**:4187-4191.
42. DANKS M, MORTON C, PAWLIK C, POTTER P: Overexpression of a rabbit liver carboxylesterase sensitizes human tumor cells to CPT-11. *Cancer Res.* (1998) **58**:20-22.
43. HAAZ M, RIVORY L, RICHE C, ROBERT J: The transformation of irinotecan (CPT-11) to its active metabolite SN-38 by human liver microsomes. Differential hydrolysis for the lactone and carboxylate forms. *Naunyn Schmiedebergs Arch. Pharmacol.* (1997) **356**:257-262.
44. GUPTA E, LESTINGI TM, MICK R, RAMIREZ J, VOKES EE, RATAIN MJ: Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res.* (1994) **54**:3723-3725.
45. DRENGLER RL, KUHN JG, SCHAAF LJ *et al.*: Phase I and pharmacokinetic trial of oral irinotecan administered daily for 5 days every 3 weeks in patients with solid tumors. *J. Clin. Oncol.* (1999) **17**:685-696.
46. RADOMSKI KM, STEWART CF, PANETTA JC, HOUGHTON PJ, FURMAN WL: Phase I and pharmacokinetic study of oral irinotecan in pediatric patients with solid tumors. *Proc. Am. Soc. Clin. Oncol.* (2000) **19**:592a.
47. SCHOEMAKER NE, MATHOT RA, SCHOFFSKI P, ROSING H, SCHELLENS JH, BEIJNEN JH: Development of an optimal pharmacokinetic sampling schedule for rubitecan administered orally in a daily times five schedule. *Cancer Chemother. Pharmacol.* (2002) **50**:514-517.
48. VERSCHRAEGEN CF, NATELSON EA, GIOVANELLA BC *et al.*: A Phase I clinical and pharmacological study of oral 9-nitrocamptothecin, a novel water-insoluble topoisomerase I inhibitor. *Anticancer Drugs* (1998) **9**:36-44.
49. VERSCHRAEGEN CF, GUPTA E, LOYER E *et al.*: A Phase II clinical and pharmacological study of oral 9-nitrocamptothecin in patients with refractory epithelial ovarian, tubal or peritoneal cancer. *Anticancer Drugs* (1999) **10**:375-383.
50. STEHLIN JS, GIOVANELLA BC, NATELSON EA *et al.*: A study of 9-nitrocamptothecin (RFS-2000) in

patients with advanced pancreatic cancer. *Int. J. Oncol.* (1999) **14**:821-831.

51. KONSTADOULAKIS MM, ANTONAKIS PT, TSIBLOULIS BG *et al.*: A Phase II study of 9-nitrocamptothecin in patients with advanced pancreatic adenocarcinoma. *Cancer Chemother. Pharmacol.* (2001) **48**:417-420.
52. RIVKIN S, BURRIS H, GERSTEIN H *et al.*: A Phase II study of rubitecan (RFS 2000, 9NC, 9-nitro-20(S)-camptothecin) in patients with refractory pancreatic cancer. *Proc. Am. Soc. Clin. Oncol.* (2000) **19**:262A.
53. HEWES H, SMITH, JA, VERSCHRAEGEN C: Clinical studies of rubitecan (9-nitro 20(*S*) camptothecin. (2005) (In press).
54. SPARREBOOM A, DE JONGE MJ, PUNT CJ *et al.*: Pharmacokinetics and bioavailability of oral 9-aminocamptothecin capsules in adult patients with solid tumors. *Clin. Cancer Res.* (1998) **4**:1915-1919.
55. DE JONGE MJA, PUNT CJ, GELDERBOLM AH *et al.*: Phase I and pharmacologic study of oral (PEG-1000) 9-aminocamptothecin in adult patients with solid tumors. *J. Clin. Oncol.* (1999) **17**:2219-2226.
56. XIONG HQ, TRAN HT, MADDEN TL *et al.*: Phase I and pharmacological study of oral 9-aminocamptothecin colloidal dispersion (NSC 603071) in patients with advanced solid tumor. *Clin. Cancer Res.* (2003) **9**:2066-2071.
57. MANI S, IYER L, JANISCH L *et al.*: Phase I clinical and pharmacokinetic study of oral 9-aminocamptothecin (NSC 603071). *Cancer Chemother. Pharmacol.* (1998) **42**:84-87.
58. GERRITS CJ, SCHELLENS JH, CREEMERS GJ *et al.*: The bioavailability if oral GI147211 (GG211), a new topoisomerase I inhibitor. *Br. J. Cancer* (1997) **76**:946-951.
59. GELDERBLOM H, SALAZAR R, VERWEIJ J *et al.*: Phase I pharmacological and bioavailability study of oral diflomotecan (BN80915), a novel E-ring-modified camptothecin analogue in adults with solid tumors. *Clin. Cancer Res.* (2003) **9**:4101-4107.
60. PRATESI G, BERETTA GL, ZUNINO F: Gimatecan, a novel camptothecin with a promising preclinical profile. *Anticancer Drugs* (2004) **15**:545-552.
61. ZHU AX, READY NE, CLARK JW *et al.*: Phase I trail of gimatecan given orally once a week for 3 of 4 weeks in patients with advanced solid tumors. *Am. Soc. Clin. Oncol.* (2003) **22**:557A.
62. GIANNI L, HESS D, BASELGA J *et al.*: A Phase I study of the oral camptothecin gimatecan with a design of concerted dose escalation in three schedules of different dosing-duration. *Proc. Am. Soc. Clin. Oncol.* (2003) **22**:554A.
63. ALDERSON L, SUPKO, MAESTRI X *et al.*: Phase I/II trail of gimatecan in patients with recurrent malignant glioma. *Proc. Am. Soc. Clin. Oncol.* (2003) **22**:A416.
64. SUPKO JG, ALDERSON L, WEN P *et al.*: Pharmacokinetics of gimatecan, an orally administered camptothecin analogue, in patients with malignant gliomas. *J. Clin. Oncol.* (2004) **22**:2039.
65. BONI C, GAMUCCI T, NONETTI A *et al.*: A Phase II study of the novel oral camptothecin ST1481 in pretreated metastatic colorectal cancer (CRC). *J. Clin. Oncol.* (2004) **22**:3684.
66. GILBERT BE, KNIGHT C, ALVAREZ FG *et al.*: Tolerance of volunteers to cyclosporine A-dilauroylphosphatidylcholine liposome aerosol. *Am. J. Respir. Crit. Care Med.* (1997) **156**:1789-1793.
67. WALDREP JC, GILBERT BE, KNIGHT CM *et al.*: Pulmonary delivery of beclomethasone liposome aerosol in volunteers. Tolerance and safety. *Chest* (1997) **111**:316-323.
68. ENGLUND JA, PIEDRA PA, AHN YM, GILBERT BE, HIATT P: High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *J. Pediatr.* (1994) **125**:635-641.
69. GILBERT BE, WYDE PR, LOPEZ-BERESTEIN G, WILSON SZ: Aerosolized amphotericin B-liposomes for treatment of systemic Candida infections in mice. *Antimicrob. Agents Chemother.* (1994) **38**:356-359.
70. KOSHKINA NV, GILBERT BE, WALDREP JC, SERYSHEV A, KNIGHT V: Distribution of camptothecin after delivery as a liposome aerosol or following intramuscular injection in mice. *Cancer Chemother. Pharmacol.* (1999) **44**:187-192.
71. KNIGHT V, KOSHKINA NV, WALDREP JC, GIOVANELLA BC, GILBERT BE: Anticancer effect of 9-nitrocamptothecin liposome aerosol on human cancer xenografts in nude mice. *Cancer Chemother. Pharmacol.* (1999) **44**:177-186.
72. KNIGHT V, KLEINERMAN ES, WALDREP JC, GIOVANELLA BC, GILBERT BE, KOSHKINA NV: 9-nitrocamptothecin liposome aerosol treatment of human cancer subcutaneous xenograft and pulmonary cancer metastases in mice. *Ann. NY Acad. Sci.* (2000) **922**:151-163.
73. GILBERT BE, SERYSHEV A, KNIGHT V, BRAYTON C: 9-nitrocamptothecin liposome aerosol: lack of subacute toxicity in dogs. *Inhal. Toxicol.* (2002) **14**:185-197.
74. VERSCHRAEGEN C, GILBERT B, HUARINGA A *et al.*: Feasibility, Phase I and pharmacological study of aerosolized liposomal 9 nitro-(20S)-camptothecin (L9NC) in patients with advanced malignancies in the lungs. *Ann. NY Acad. Sci.* (2000) **922**:352-354.
75. VERSCHRAEGEN C, GILBERT B, LOYER E *et al.*: Clinical evaluation of the delivery and safety of aerosolized liposomal 9 nitro-(20*S*)-camptothecin (L9NC) in patients with advanced pulmonary malignancies. *Clinical Cancer Research* (2004) **10**:2319-2326.
76. LAWSON KA, ANDERSON K, SNYDER RM *et al.*: Novel vitamin E analogue and 9-nitro-camptothecin administered as liposome aerosols decrease syngeneic mouse mammary tumor burden and inhibit metastasis. *Cancer Chemother. Pharmacol.* (2004) **5A**(5):421-431.
77. GAUTAM A, WALDREP JC, DENSMORE CL *et al.*: Growth inhibition of established B16-F10 lung metastases by sequential aerosol delivery of p53 gene and 9-nitrocamptothecin. *Gene Ther.* (2002) **9**:353-357.
78. BLANEY SM, COLE DE, BALIS FM, GODWIN K, POPLACK DG: Plasma and cerebrospinal fluid pharmacokinetic study of topotecan in nonhuman primates. *Cancer Res.* (1993) **53**:725-727.
79. BERG SL, BALIS FM, ZIMM S *et al.*: Phase I/II trial and pharmacokinetics of intrathecal diaziquone in refractory meningeal malignancies. *J. Clin. Oncol.* (1992) **10**:143-148.

80. BLANEY SM, BALIS FM, POPLACK DG. Pharmacologic approaches to the treatment of meningeal malignancy. *Oncology (Huntingt)* (1991) **5**:107-116.

81. CHAMBERLAIN MC, KHATIBI S, KIM JC, HOWELL SB, CHATELUT E, KIM S: Treatment of leptomeningeal metastasis with intraventricular administration of depot cytarabine (DTC 101). A Phase I study. *Arch. Neurol.* (1993) **50**:261-264.

82. MCCULLY CL, BALIS FM, BACHER J, PHILLIPS J, POPLACK DG: A rhesus monkey model for continuous infusion of drugs into cerebrospinal fluid. *Lab. Anim. Sci.* (1990) **40**:520-525.

83. BLANEY SM, COLE DE, GODWIN K, SUNG C, POPLACK DG, BALIS FM: Intrathecal administration of topotecan in nonhuman primates. *Cancer Chemother. Pharmacol.* (1995) **36**:121-124.

84. BLANEY S, EIDEMAN R, BERG S *et al.*: Phase I clinical trail of intrathecal topotecan in patients with neoplastic meningitis. *J. Clin. Oncol.* (2003) **21**:143-147.

85. BLANEY SM, TAKIMOTO C, MURRY DJ *et al.*: Plasma and cerebrospinal fluid pharmacokinetics of 9-aminocamptothecin (9-AC), irinotecan (CPT-11), and SN-38 in nonhuman primates. *Cancer Chemother. Pharmacol.* (1998) **41**:464-468.

86. PLAXE SC, CHRISTEN RD, O'QUIGLEY J *et al.*: Phase I and pharmacokinetic study of intraperitoneal topotecan. *Invest. New Drugs* (1998) **16**:147-152.

87. HOFSTRA LS, BOS AM, DE VRIES EG *et al.*: Phase I and pharmacokinetic study of intraperitoneal topotecan. *Br. J. Cancer* (2001) **85**:1627-1633.

88. ROBERTSON MD, MALPASS TW, MCGONIGLE KD, WEIDEN PL, MUNTZ H: Phase II study of intraperitoneal topotecan as consolidation chemotherapy in ovarian cancer. *J. Clin. Oncol.* (2004) **22**:5077.

89. MUGGIA F, LIEBES L, HAZARIK M *et al.*: Phase I and pharmacologic study of i.p. 9-aminocamptothecin given as six fractions over 14 days. *Anticancer Drugs* (2002) **13**:819-825.

90. CHOI SH, TSUCHIDA Y, YANG HW: Oral versus intraperitoneal administration of irinotecan in the treatment of human neuroblastoma in nude mice. *Cancer Lett.* (1998) **124**:15-21.

91. GUICHARD S, CHATELUT E, LOCHON I, BUGAT R, MAHJOUBI M, CANAL P: Comparison of the pharmacokinetics and efficacy of irinotecan after administration by the intravenous versus intraperitoneal route in mice. *Cancer Chemother. Pharmacol.* (1998) **42**:165-170.

92. MATSUI A, OKUDA M, TSUJITSUKA K, ENOMOTO K, MARUYAMA K: Pharmacology of intraperitoneal CPT-11. *Surg. Oncol. Clin. N. Am.* (2003) **12**:795-811.

93. PROULX ME, DESORMEAUX A, MARQUIS JF, OLIVIER M, BERGERON MG: Treatment of visceral leishmaniasis with sterically stabilized liposomes containing camptothecin. *Antimicrob. Agents Chemother.* (2001) **45**:2623-2627.

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