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REVIEW

Lalitha Iyer · Mark J. Ratain

Clinical pharmacology of camptothecins

Abstract Camptothecins (CPTs) are a unique class of chemotherapeutic agent which inhibit DNA synthesis by inhibiting topoisomerase I activity. Structure-activity studies on the original CPT alkaloid led to the development of the new analogues irinotecan (CPT-11), topotecan, and 9-aminocamptothecin, which have improved water solubility and lower toxicity. CPT analogues exhibit interesting pharmacokinetic/pharmacodynamic and metabolic properties that are of major research and clinical interest. This review describes the clinical pharmacology of these 3 CPT analogues. Specific areas such as absorption after extravascular administration, pharmacokinetic/pharmacodynamic variability, metabolism, and administration in special populations are discussed.

Key words Camptothecins · Irinotecan · Topotecan · 9-Aminocamptothecin · Clinical pharmacology

Introduction

Camptothecin (CPT) (Fig. 1) is a cytotoxic alkaloid extracted from the bark, fruit, and leaves of the Chinese tree Camptotheca acuminata. Wall and coworkers were the first to isolate the alkaloid and demonstrate its promising antineoplastic activity [131]. Despite encouraging results in the initial clinical trials [39, 81] with camptothecin sodium (NSC-100880), its development was hampered by severe toxicities such as hemorrhagic cystitis and diarrhea [78]. Subsequently, there was a renewed interest in the clinical development of CPT as a result of the understanding of the role of topoisomerase I enzyme in its antitumor activity [50, 54] and the synthesis of structural analogues of CPT with greater water solubility and lower toxicities [34, 134, 135]. These analogues, irinotecan, topotecan, 9-aminocamptothecin (9-AC, NSC 603071), 9-nitrocamptothecin (9-NC), and lurtotecan (GI 147211) (Fig. 1), contain structural modifications to the A- and B-rings of CPT. This review focuses on the clinical pharmacology of some of these improved CPTs: irinotecan, 9-AC, and topotecan.

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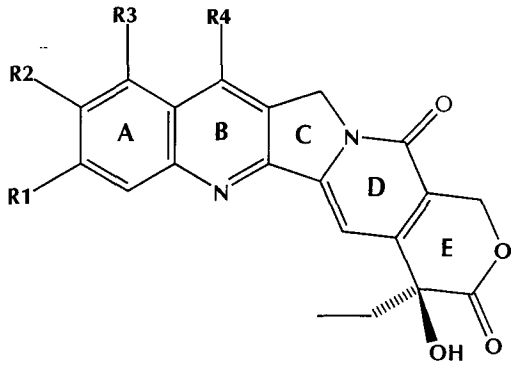
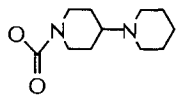
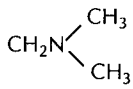
Mechanism of action

CPTs inhibit the activity of topoisomerase I and are primarily active in the S-phase of the cell cycle [69, 71]. Topoisomerase I is critical for cell growth and proliferation. It makes a transient single-strand break in the supercoiled DNA duplex resulting in relaxation of supercoiled DNA [2]. CPTs stabilize the covalent cleavable DNA–topoisomerase I complex causing arrest of the replication fork, which in turn results in inhibition of DNA synthesis and ultimately cell death [54, 55].

An intact lactone group in the E-ring of CPT is required for optimal inhibition of topoisomerase I activity [51]: opening of the lactone (closed) form to the hydroxy-acid (open) form leads to a loss of pharmacologic activity. In addition, the (S) stereochemistry and -OH group in position 20 are essential for optimal anticancer activity [51, 134]. Topoisomerase I is overexpressed in certain tumor types, including colorectal and cervical tumors [38, 75], when compared with corresponding nonmalignant cells. This finding has generated a special interest in developing CPT analogues to target tumors such as colorectal cancer.

Fig. 1 Structures of CPT and its analogues irinotecan, topotecan, lurtotecan, 9-AC, and 9-nitro-camptothecin



Compound	R1 (C-11)	R2 (C-10)	R3 (C-9)	R4 (C-7)
Camptothecin	H	H	H	H
Irinotecan	H		H	CH_2CH_3
Topotecan	H	OH		H
Lurtotecan			H	
9-Aminocamptothecin	H	H	NH_2	H
9-Nitrocamptothecin	H	H	NO_2	H

Irinotecan

During the search for water-soluble analogues of CPT, several derivatives with an intact δ-lactone ring were investigated. This led to the development of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11) or irinotecan (Fig. 1) [22]. In preclinical studies, irinotecan exhibited greater antitumor activity than CPT or doxorubicin in a variety of murine tumors, both in ascites and in solid forms, when administered by various routes [4, 68]. Irinotecan also demonstrated significant antitumor activity against colorectal, small cell and non-small cell lung, cervical, breast, and ovarian cancers in human tumor cloning assays [9, 111].

Bioanalytical method

CPT and its analogues undergo reversible hydrolysis from the lactone to the open form at elevated pH (>7.0). As the lactone form is the pharmacologically active entity, efforts have been made to introduce additional steps in the analytical procedure to separate lactone and open forms of irinotecan and its active metabolite 7-ethyl-10-hydroxy camptothecin (SN-38) [94], as well as topotecan [8] and 9-AC [119]. However, these methods include sample treatment with acids to estimate total drug, with the open form subsequently being estimated by subtraction. This can be cumbersome and requires immediate processing of plasma samples. Variations in hydrolysis rates could lead to instability of the lactone forms. In addition, lactone forms of CPT analogues are generally bound to plasma proteins to a greater extent than the corresponding hydroxy acid forms, and there may be variations in free lactone concentrations due to interindividual differences in plasma protein concentrations and lactone-protein binding capacity. If the

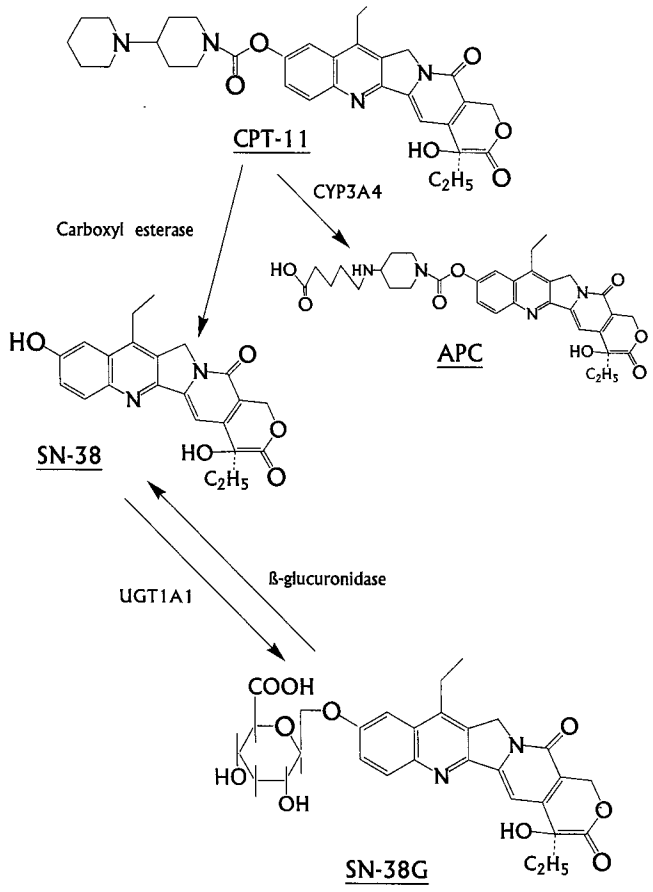


Fig. 2 Metabolism of irinotecan to APC, SN-38, and SN-38G

interconversion between lactone and hydroxy acid forms is predominantly determined by pH, the ratio of free lactone to free open forms must be relatively constant. Hence, quantitation of total concentrations of CPT and its analogues should be adequate for correlation of pharmacokinetics with clinical outcomes. Moreover, certain studies have shown that total drug may be more predictive of drug effect in the case of topotecan [40], and the areas under the curve (AUCs) for total forms correlate significantly with the AUC of lactone forms, as seen with irinotecan and SN-38 [106].

Reverse-phase high-performance liquid chromatography (HPLC) methods coupled with fluorescence detection have been used for the quantitation of irinotecan and its metabolites in biological fluids. Rivory and Robert [94] introduced the use of an ion-pairing agent, tetrabutylammonium phosphate (TBAP), for the simultaneous determination of open and closed forms of irinotecan using fluorescence detection at 355 nm (excitation) and 515 nm (emission). Barilero et al. [5] used a solid-phase extraction method to determine SN-38 and irinotecan simultaneously in plasma samples at 380 nm (excitation) and 500 nm (emission). Most clinical studies have used slight modifications of the above methods, using CPT as the internal standard. For the determination of 10-O-glucuronyl-SN-38 (SN-38G), samples are incubated with β-glucuronidase enzyme, and then subjected to HPLC assay. SN-38G concentrations are then determined as "SN-38 equivalents" calculated from the increase in SN-38 concentrations due to treatment with β-glucuronidase. SN-38G may also be quantitated directly using fluorescence measurements at 355 nm (excitation) and 515 nm (excitation) [56].

Absorption

The pharmacokinetics of irinotecan after oral administration are being studied extensively [71]. In mice, molar ratios of SN-38 AUC/irinotecan AUC were at least 3-fold greater after oral irinotecan administration compared to equivalent intravenous doses, indicating a higher exposure of SN-38 due to first-pass metabolism [116]. This ratio decreased at higher doses of irinotecan, possibly due to saturation of conversion of irinotecan to SN-38 by carboxylesterase (CE) [116]. Significant grade 4 diarrhea and neutropenia were observed after oral irinotecan 100 mg/m^2/day on a daily × 5 every 3 weeks schedule [32].

Metabolism

Irinotecan undergoes sequential metabolism to SN-38 by tissue and serum CEs and to SN-38G by hepatic uridine diphosphate glucuronosyltransferases (UGTs) (Fig. 2). UGT1A1 has recently been shown to glucuronidate SN-38 to SN-38G [58–60]. K_m values of 0.28 μM and 4.1 μM have been reported for CE [122] and UGT [56], respectively.

SN-38 is the active metabolite of irinotecan, with 100- to 1000-fold greater antitumor activity than irinotecan [64, 65]. Recently, an additional metabolite of irinotecan was identified in plasma from irinotecan-treated patients [96]. This metabolite {7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin; APC is formed from irinotecan by cytochrome P450 3A4 (CYP3A4) (Fig. 2) [47]. APC has been shown to be about 500-fold less potent than SN-38 in terms of antitumor activity [96].

SN-38 and SN-38G undergo significant biliary excretion and enterohepatic circulation. SN-38G may be deconjugated to form SN-38 by intestinal β-glucuronidase [61, 118].

The severe diarrheal episodes caused by irinotecan are related to its metabolism, as the active metabolite, SN-38, has been shown to accumulate in the intestine after intraperitoneal irinotecan administration to athymic mice [3]. Gupta et al. [41] have shown that glucuronidation of SN-38 may protect against irinotecan-induced gastrointestinal toxicity. The clinical significance of UGT1A1 polymorphism in the metabolism of irinotecan is discussed below.

Pharmacokinetics

Irinotecan entered clinical trials in the USA in 1991 after undergoing some clinical investigation in Japan (1986) and France (1990) [43, 97, 98, 100]. Most trials have used the continuous infusion (CI) route at weekly intervals for 4

Table 1 Pharmacokinetic parameters of irinotecan (total) from major clinical trials

Dose (mg/m^2)	Schedule	*n*	Terminal $t_{1/2}$ (h)	C_{max} (μg/ml)	Clsys ($l/h/m^2$)	Vd_{ss} (l/m^2)	Reference
50–150	90-min i.v. infusion, weekly	17	2.8 (1.5–4.3)	0.61–2.97	16.75 (13.3–21.5)	–	82
25–40	5-day i.v. infusion	24	26.55 (16.1–37.7)	0.12–0.20	–	–	83
50–180	30–90-min i.v. infusion, weekly × 4, every 6 weeks	17	7.9±2.8	0.89–1.97	15.3±3.5	–	99
50–145	30–90-min i.v. infusion, weekly × 3, every 5 weeks	47	9.3±0.5	0.67–2.58	15±0.8		31
100–345	90-min i.v. infusion, every 3 weeks	31	5.2	1.8–4.5 μmol/l	0.35±0.03	148±20	102
100–750	30-min i.v. infusion, every 3 weeks	64	14.2±0.9	2.3–17.3	15±1.0	157±8.0	1
100	90-min i.v. infusion, weekly × 4, every 6 weeks	36	7.2	0.74–2.31	–	–	105
145	90-min i.v. infusion, weekly × 4, every 6 weeks	40	8.8±4.3	0.83–3.58	14.6±6.4	136±73.9	46

Table 2 Pharmacokinetic parameters of SN-38 (total) from major clinical trials

Dose (mg/m^2)	Schedule	*n*	Terminal $t_{1/2}$ (h)	C_{max} (μg/ml)	AUC (μg.h/ml)	Reference
50–150	90-min i.v. infusion, weekly	17	6.75 (3.0–10.2)	0.018–0.032	0.12–0.35	82
25–40	5-day i.v. infusion	24	29.6 (24±39)	0.007–0.01	0.86–1.08	83
50–180	90-min i.v. infusion, weekly × 4, every 6 weeks	17	13±5.8	0.26–0.039	0.215–0.449	99
50–145	30–90-min i.v. infusion, weekly × 3, every 5 weeks	47	7.7±0.9	0.01–0.075	0.036–0.443	31
100–345	90-min i.v. infusion, every 3 weeks	31	5.9	75–191 μmol/l	51±3 μmol-min/l	102
100–750	30-min i.v. infusion, every 3 weeks	64	13.8±1.4	0.032–0.299	0.160–2.370	1
100	90-min i.v. infusion, weekly × 4, every 6 weeks	36	10.5	0.01–0.07	0.10–0.35	105
145	90-min i.v. infusion, weekly × 4, every 6 weeks	40	11.6±8.2	0.013–0.060	0.053–2.422	46

weeks followed by a rest period of 2 weeks, while other trials have used a once every 3 weeks dosage schedule (Table 1). The various dosage schedules and pharmacokinetic parameter estimates of irinotecan and SN-38 determined in major clinical trials are listed in Tables 1 and 2, respectively.

Terminal elimination half-life ($t_{1/2}$) values of about 5–14 h have been reported for irinotecan in clinical trials using the 30- or 90-min CI schedules. When infused continuously for 5 days [83] a much higher $t_{1/2}$ of about 27 h was obtained. Attempts have been made to fit the plasma irinotecan concentration-time data to 2- and 3-compartment models. For example, Rowinsky et al. [104] determined α and β half-lives of 4.9 min and 3.9 h, respectively, after fitting the data to a 2-compartment model equation. A triexponential model was described by de Forni et al. [31] and α, β, and γ half-lives of 6.7 min, 2 h, and 9.3 h, respectively, were obtained. The large volumes of distribution (>140 l/m^2) reported for irinotecan (Table 1) indicate significant binding to the tissue compartment.

There is considerable variation in the half-lives obtained for SN-38 (Table 2), perhaps due to the significant variability in its rate of glucuronidation. In general, SN-38 C_{max} is >100-fold lower than the corresponding values for irinotecan. One study has reported a statistically significant correlation between the irinotecan AUC and the corresponding SN-38 AUC [31]. Plasma concentrations of SN-38G were higher than corresponding concentrations of SN-38 in these studies [41, 95], with SN-38G AUCs being at least 10-fold higher than those for SN-38.

The dose dependency of irinotecan clearance is unclear because conflicting data have been published. Dose escalation from 100 to 750 mg/m^2 resulted in a >50-fold reduction in CPT clearance from 26 to 12 $l/m^2/h$ in one study [1]. Decreases in clearance estimates have also been reported by Negoro et al. [84] (0.35 to 0.22 $l/m^2/h$) and by Gupta et al. [41] (20 to 13 $l/m^2/h$). Several other studies have reported constant rates of clearance over a 4-fold irinotecan dose range [31, 99, 102]. Irinotecan has been reported to exhibit nonlinear pharmacokinetics in rats [62]. The nonlinearity in irinotecan disposition and the conflicting literature reports are not surprising, and saturation of irinotecan metabolic pathways and biliary transport mechanisms may explain these findings.

Modulation of irinotecan pharmacokinetics by coadministration of cyclosporine A (CSA) was studied in rats by

Table 3 Major toxicities of irinotecan reported at MTD/RPTD in clinical trials (*MTD* maximum tolerated dose, *RPTD* recommended phase II dose)

Dose (mg/m^2)	Schedule	MTD/RPTD (mg/m^2)	Grade 3–4 diarrhea (%)	Grade 3–4 neutropenia (%)	Grade 3–4 leukopenia (%)	Reference
50–150	90-min i.v. infusion, weekly	100	25.0	–	–	82
25–40	5-day i.v. infusion	40	66.7	–	33.3	83
50–180	90-min i.v. infusion, weekly × 4, every 6 weeks	150	16.7	16.7	–	99
50–145	30–90-min i.v. infusion, weekly × 3, every 5 weeks	145	57.1	14.2	57.1	31
100–345	90-min i.v. infusion, every 3 weeks	240	7.7	23.1	–	102
100–750	30-min i.v. infusion, every 3 weeks	600	14.2	14.2	14.2	1
100	90-min i.v. infusion, weekly × 4, every 6 weeks	100	22.2	–	13.8	105

Gupta et al. [42]. In these studies, clearance of irinotecan and its metabolites was reduced due to CSA-induced decreased biliary excretion. Based upon these results, a phase I trial of irinotecan administered with CSA has been initiated at the University of Chicago [35]. Preadministration of CSA resulted in a 30% decrease in plasma clearance of irinotecan at a 100 mg/m^2 dose administered weekly for 4 weeks. The maximum tolerated dose (MTD) was determined to be 60 mg/m^2, with leukopenia being the dose-limiting toxicity [Fagbemi S et al., unpublished results].

Considerable interpatient variability in irinotecan and SN-38 pharmacokinetics and toxicity is characteristic of irinotecan therapy. This could largely be due to pharmacogenetic differences between individuals in the metabolism of irinotecan. Our recent finding that UGT1A1 glucuronidates SN-38 is a major breakthrough in understanding these variations [L. Iyer et al., unpublished results]. SN-38 glucuronidation may be pharmacologically manipulated. For example, in a recent study, irinotecan administration in rats pretreated with valproic acid and phenobarbital resulted in inhibition and induction of SN-38G formation, respectively [45].

Pharmacogenetic differences in UGT1A1 expression and activity may lead to variations in SN-38 glucuronidation rates and variations in irinotecan pharmacokinetics and toxicity. UGT1A1 is also responsible for bilirubin glucuronidation in humans [14], and is absent in individuals with Crigler-Najjar type I (CN-I) syndrome [13, 28]. Patients exhibiting UGT1A1 polymorphism, such as those with Gilbert's syndrome [37, 79], may be at increased risk for irinotecan-induced gastrointestinal toxicity [133]. The specific molecular defect in Gilbert's syndrome is the presence of a $A(TA)_7TAA$ fragment in the UGT1A1 promoter instead of the $A(TA)_6TAA$ segment that is present in healthy individuals [15, 79]. There appears to be wide variation in the incidence of Gilbert's syndrome, ranging from 0.5% to 15% in various groups. A genotyping test has recently been developed to identify polymorphisms in the promoter region of UGT1A1 [79; L. Iyer et al., unpublished results]. Preliminary results from in vitro metabolism studies indicate a significant correlation between SN-38 glucuronidation rates and UGT1A1 genotype [L. Iyer et al., unpublished results]. The incidence of $A(TA)_7TAA$ homozygotes in the donor livers tested ($n = 29$) was 14%. These findings may enable the individualization of irinotecan therapy using pharmacogenetically derived doses, which may improve the narrow therapeutic index of this agent.

Pharmacodynamics and toxicity

The major dose-limiting toxicities of irinotecan are diarrhea and myelosuppression. Other toxicities reported include nausea, emesis, alopecia, asthenia, abdominal pain, and anemia [31]. Table 3 lists the incidence of diarrhea, leukopenia, and neutropenia at the MTD or recommended phase II dose (RPTD) determined in some of the major clinical trials.

Irinotecan-induced diarrhea usually occurs in 2 stages: an early stage which is due to a cholinergic syndrome produced by CPTs by inhibition of acetylcholine esterase [66]; and delayed diarrhea which is hypothesized to be due to direct enteral injury caused by SN-38 and irinotecan [3]. There appears to be a dose-dependent increase in the incidence of diarrhea, as 34%, 50%, and 100% of patients developed grade 3–4 diarrhea at dose levels of 100 mg/m^2, 125 mg/m^2, and 175 mg/m^2 [41]. Gupta et al. [41] introduced a surrogate measure of biliary SN-38 excretion, known as the biliary index (BI), which is determined from $AUC_{irinotecan} \times AUC_{SN\text{-}38}/AUC_{SN\text{-}38G}$. A significant correlation was found between the BI and severity of diarrhea in irinotecan-treated patients.

Several investigators have used pharmacodynamic models to relate irinotecan pharmacokinetic parameters with toxicities [42]. Sigmoidal E_{max} models have been used to describe relationships between percentage decreases in absolute neutrophil counts and diarrhea versus irinotecan and SN-38 AUCs [1, 23, 102]. Other investigators have used linear models to describe these relationships [31, 105].

Limited sampling models

Limited sampling models (LSMs) have been used to estimate pharmacokinetic parameters and the toxicity of irinotecan and SN-38 [21, 76, 107]. Sasaki et al. [107] used 2 sampling points at 2.5 h and 13.5 h to predict the irinotecan and SN-38 AUC accurately. Other investigators have used a trivariate model based on sampling times of 0.5 h, 1 h, and 6 h to predict the SN-38 and irinotecan AUC [21]. Mick et al. [76] have used LSMs with time points of 3.0 h and 11.5 h, 3.5 h and 11.5 h, and 9.5 h and 11.5 h to estimate the AUC for irinotecan, SN-38, and SN-38G adequately.

Using a Bayesian algorithm, Yamamoto et al. [137] have recently described LSMs using sampling times of 4 and 8 h after irinotecan infusion on days 1 and 3. In this study, irinotecan (60 mg/m^2) was administered as a 90-min CI after etoposide 60 mg/m^2 infusion for 60 min for 3 consecutive days. The irinotecan AUC correlated significantly with degree of leukopenia, neutropenia, and nausea/vomiting, but not with severity of diarrhea or response.

Special populations

Vassal et al. [128] have recently established the efficacy of irinotecan in peripheral primitive neuroectodermal tumor (pPNET) and neuroblastoma xenografts in mice. This finding indicates that irinotecan may be an interesting new drug in pediatric oncology because neuroblastomas account for 6–8% of all malignancies in children [128]. Irinotecan also produced significant growth delays in human tumor xenografts derived from pediatric central nervous system malignancies, such as gliomas, medulloblastomas, and ependymomas, transplanted into mice [48]. No major differences in pharmacokinetic parameters of irinotecan have been reported between colorectal cancer patients $\geq$65 and $<$65 years of age [108]. No significant gender or race (Caucasian vs black) differences have been reported for irinotecan pharmacokinetics or toxicity [92].

9-AC

9-AC has an amino group substituted in position C-9 in the A-ring of CPT (Fig. 1). It has demonstrated high antitumor activity against lung, breast, and melanoma xenografts, hepatic metastases of primary colon tumors, and intraperitoneally implanted leukemias and sarcomas [80, 86–89, 135]. 9-AC has been shown to induce disease-free remissions in mice with colon cancer xenografts [38].

The major disadvantage with 9-AC relates to its formulation: it is the most poorly water-soluble analogue of CPT. 9-AC was initially formulated in dimethylacetamide (DMA) using a special diluent (NSC 651935) consisting of 51% polyethylene glycol 400 and 49% 0.01 M phosphoric acid [24]. Due to incompatibility with aqueous solutions and adherence to plastic surfaces, a new lipid colloidal dispersion (CD) formulation of 9-AC in dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol has recently been developed which has a particle size of <3 μm and is compatible with aqueous solutions and more stable [70]. More recent clinical trials have been employing the CD formulation of 9-AC [33, 73].

Bioanalytical method

Measurement of 9-AC in biological fluids is usually performed using reverse-phase HPLC separation and fluorescence detection [117, 119]. Supko and Malspeis [117] introduced a method to improve the relatively poor fluorescence of 9-AC lactone (in comparison with CPT) using postcolumn acidification with trifluoroacetic acid, with a lower limit of quantification of 13 nm in human plasma samples. Takimoto et al. [119] have introduced a solid-phase extraction method to separate the 9-AC lactone form from the carboxylate form which has an improved sensitivity of 0.25 nm.

Metabolism

The results from clinical studies such as the CI studies in humans indicate no major metabolism of 9-AC [29]. No glucuronide formation, similar to SN-38, was detected by incubating plasma samples from 9-AC-treated patients with β-glucuronidase [120]. However, systematic studies designed to investigate possible 9-AC metabolism have not been performed in vitro using hepatic cellular or subcellular fractions.

Pharmacokinetics and toxicity

The DMA formulation of 9-AC was administered as a 72-h continuous intravenous infusion in a phase I clinical trial [103] at doses of 5 to 60 μg/m^2/h ($n = 31$). A terminal $t_{1/2}$ of about 36 h was determined at the 45 and 60 μg/m^2/h doses, indicating a longer half-life than that of the more water-soluble CPT analogues irinotecan and topotecan. Significant variations in plasma 9-AC lactone levels and volumes of distribution were noted; these were attributed to possible interindividual differences in protein binding [103]. Minimal gastrointestinal toxicities were reported in this trial. Neutropenia was the dose-limiting toxicity and the MTD was 45 μg/m^2/h. Minor responses were observed in 3 patients.

Results from another ongoing phase I 9-AC (72-h CI) clinical trial from the Harvard/Phase I Oncology program [33] suggest at least a 20% increase in MTD for the CD formulation of 9-AC. In addition, a shorter $t_{1/2}$ of about 14 h was found in this study, which may be due to the use of the revised assay methodology [119] and is in agreement with results from other investigations [29].

The clinical pharmacology of 9-AC administered as a 72-h CI every 14 days in 48 patients at a dose range of 5 to

47 μg/m²/h was studied by Takimoto et al. [120, 121]. Only about 10% of total plasma 9-AC circulated in the active lactone form, which is lower than that reported for SN-38 and topotecan. Total 9-AC clearance increased more than 2-fold at higher doses, indicating nonlinear pharmacokinetics [121]. However, clearance of 9-AC lactone was uniform with increasing doses (24.5 ± 7.3 l/h/m²) [29]; terminal $t_{1/2}$ values of 11.1 ± 4.5 h were determined in this study using the DMA formulation of 9-AC. Dose-limiting myelosuppression was observed, with 9-AC doses of 35 μg/m²/h without G-CSF or 47 μg/m²/h with G-CSF support being recommended for phase II studies [29]. Repeated administration of 9-AC in 3 patients showed no evidence of drug accumulation after multiple cycles of 2 weeks each [121].

Sixteen patients were treated with oral 9-AC (CD formulation) at the University of Chicago using doses of 0.2 to 0.68 mg/m²/day for 5 days repeated every other week [73]. There was significant interpatient variability in C_{max} and $AUC_{0-\infty}$ at each dose level, and these parameters exhibited poor correlations with dose (r^2 = 0.57 and r^2 = 0.34, respectively). Fatigue and anorexia were the most common side effects noted. This study was discontinued for ethical reasons as the formulation was considered unsuitable for further clinical development. The considerable intersubject variations in 9-AC pharmacokinetics and low 9-AC exposure after oral administration may have been due to a combination of factors such as saturable absorption and/or elimination, polymorphism in gut enzymes leading to differential formation of any unknown metabolites of 9-AC, and differences in protein-binding capacities. Newer formulations such as soft gelatin capsules are being developed for oral administration of 9-AC [114]. Preliminary results indicate oral bioavailability of 27–49% using this formulation [114].

Pharmacodynamics

Pharmacodynamic analysis in the 72-h CI study [121] indicated a strong correlation between dose-limiting neutropenia and steady-state plasma 9-AC lactone concentrations (C_{ss}) (r^2 = 0.77) and 9-AC dose administered (r^2 = 0.71). The relationship between degree of hematologic toxicity and C_{ss} values was best described using a sigmoidal E_{max} model [121]. Weaker correlations were obtained between C_{ss} (9-AC lactone) and thrombocytopenia (r^2 = 0.36). Total bilirubin, albumin, and age were also found to be predictive of neutropenia and thrombocytopenia in a sigmoidal E_{max} model developed by Minami et al. [77]. 9-AC concentrations were not significantly better than dose in predicting toxicity in this study.

Special populations

The fate of nonrenally cleared 9-AC is unknown. If most 9-AC is renally cleared, it is logical to expect that dose reductions will be necessary in patients with compromised renal function, although clinical studies addressing this issue have not yet been designed. In the phase I clinical studies by Takimoto et al. [121], there was no correlation between either renal or hepatic function and any pharmacokinetic or pharmacodynamic parameter, although the sample size was small due to the exclusion of patients with severe organ dysfunction from this study. Age and gender differences in the clinical pharmacology of 9-AC have not yet been determined.

Topotecan

Topotecan [(S)-9-dimethyl-aminomethyl-10-hydroxy-camptothecin hydrochloride] has a stable basic chain (dimethylaminomethyl) substituted in the 9th position of the A-ring of camptothecin (Fig. 1) [7, 26, 49, 60]. Topotecan exhibited activity against tumor xenografts in mice as well as significant in vitro activity against breast, colon, kidney, lung, and ovarian tumor colony-forming units [18, 130]. It has now been approved in the USA for clinical use as second-line therapy in metastatic ovarian cancer [6].

Bioanalytical method

Similar to irinotecan, SN-38, and 9-AC, topotecan concentrations are measured in biological fluids using a reverse-phase HPLC assay method. Beijnen and coworkers [8] developed a method to deproteinize plasma with cold methanol, which stabilizes the lactone and acid forms of topotecan. Fluorescence detection at 381 nm (excitation) and 527 nm (emission) was used after HPLC separation, with a lower limit of quantitation of 0.05 ng/ml. Other investigators have utilized solid-phase extraction to isolate the lactone form, followed by acidification to measure total topotecan [43].

Absorption

The bioavailability and efficacy of oral administration of topotecan have been studied extensively [16, 20, 27, 67, 74, 110]. Using murine tumor models, McCabe and Johnson [74] demonstrated an oral topotecan bioavailability of 28%, using AUC values from intraperitoneal topotecan administration for comparison. In this study, oral topotecan was as effective as parenteral topotecan in inhibiting tumor growth and was tolerated at about 1.7-fold the MTD obtained after parenteral administration. Oral topotecan had a bioavailability of 44% in humans and exhibited efficacy comparable to that of topotecan administered by continuous intravenous infusion [67]. Schellens et al. [110] have reported an oral bioavailability of 21–45% after single-dose (1.5 mg/m²) administration in humans. However, the same group had earlier reported significant diarrhea and myelosuppression after chronic oral dosing of topotecan at doses of 0.4–0.6 mg/m², indicating significant differences in safety

Table 4 Pharmacokinetic parameters of topotecan (total) from major clinical trials

Dose (mg/m^2)	Schedule	*n*	Terminal $t_{1/2}$ (h)	C_{max} (ng/ml)	Clsys ($l/h/m^2$)	Vd_{ss} (l/m^2)	Reference
2.5–22.5	30-min i.v. infusion, every 3 weeks	17	4.3±1.8	185–778	8.0±3.1	40±1.8	132
0.5–2.5	30-min i.v. infusion, daily × 5, every 3 weeks	12	2.9±0.7	–	30±11	25±19	40
1.25–1.5	30-min i.v. infusion, daily × 5	10	3.4*	59–65*	21*	84.5*	104
1.2–2.0	24-h i.v. infusion, weekly	21	3.5	3.7–6.7	14.0	–	46
0.5–1.5	24-h i.v. infusion, daily × 5, every 3 weeks	34	2.25	33.9–73.4[a]	33	72.68	126

* Median value
[a] nM

profiles between single-dose and repetitive oral dosing of topotecan [109].

Compared with other camp to the cins, topotecan has also shown measurable penetration into the cerebrospinal fluid (>30%) in nonhuman primates, and therefore has been suggested as a potential alternative in refractory meningeal tumors [11, 12]. Intraperitoneal administration has been suggested for the treatment of ovarian cancer confined to the peritoneal cavity due to its promising antitumor activity in mice with ovarian carcinoma xenografts [91].

Metabolism

No metabolites of topotecan have been identified to date, although some demethylation has been suggested to occur [49, 93]. There is speculation that topotecan may undergo (CYP 3A-catalyzed metabolism [49], as its clearance is altered significantly by coadministration of CYP3A inhibitors and inducers in pediatric patients [115]. Topotecan has been reported to be excreted unchanged into the urine in amounts ranging from 25% to 90% of the administered dose depending upon the dosing schedule [49, 104, 129]. Despite large urinary excretion, topotecan, unlike CPT, does not produce urinary toxicity due to its greater water solubility and consequent lack of precipitation in urine [49]. There also appears to be some biliary excretion of topotecan, with peak biliary concentrations being about 1.5-fold greater than corresponding plasma concentrations [132].

Pharmacokinetics

The pharmacokinetics of topotecan have been studied in humans using various infusion schedules. Table 4 lists the pharmacokinetic data obtained from clinical trials. Topotecan has a relatively short half-life (2 to 4 h) compared with irinotecan and 9-AC. Longer infusions for 3, 5, and 21 days were designed to increase the $t_{1/2}$ of topotecan and to achieve a higher dose intensity [19, 52, 63], but resulted in little influence on the dispositional characteristics of topotecan [43].

Steady-state and maximal concentrations of topotecan and AUC values correlate linearly with dosage, indicating linear pharmacokinetics [10, 49, 52, 126, 132]. The ratio of lactone to total topotecan AUC was also relatively constant (about 0.3) over a dose range of 2.5 to 22.5 mg/m^2 [49, 132]. However, nonlinear increases in C_{ss} and AUC values have been reported in a phase I study of topotecan administered as a 24-h CI [125]. No significant accumulation of topotecan was observed during 21-day CI [49] or 30-min infusion for 5 days [49, 101, 104, 126].

Steady-state volumes of distribution of topotecan range from about 25 to 75 l/m^2, indicating extensive binding to tissue components (Table 4) [49]. Relatively less plasma protein binding (21%) has been reported for topotecan in humans [132] compared with 9-AC, irinotecan, and SN-38. Erythrocytes act as a depot for topotecan (lactone), with C_{ss} values almost 1.7-fold those obtained in plasma [25]. The total body clearance of total topotecan from plasma ranged from 8 to 33 $l/h/m^2$ (Table 4), and has been reported to be independent of the administered dose [101, 126].

Pharmacodynamics and toxicity

The major dose-limiting toxicities of topotecan are neutropenia and to a lesser extent thrombocytopenia [17, 26, 131]. Reported nonhematologic toxicities include nausea (12%), vomiting (10%), fatigue (3%), and alopecia (11%) [26].

Pharmacokinetic/pharmacodynamic models have been used to predict hematological toxicities using pharmacokinetic measurements. Grochow et al. [40] have used a sigmoidal E_{max} model to relate change in absolute neutrophil count to topotecan dosage, using a 30-min intravenous infusion for 5 days. A dose of 0.9 mg/m^2/day was found to produce a 50% decrease in absolute neutrophil count. The sigmoidal E_{max} model could also predict changes in neutropenia in patients who received topotecan dose escalations or reductions [40, 101], and indicated a lack of cumulative toxicity. This was confirmed by the results from a 24-h CI once-weekly dosing schedule, which showed a correlation between total and lactone AUC and C_{new} Ha values and decrease in absolute neutrophil counts on days 15, 22, and 29 [46]. The derived pharmacodynamic parameters from sigmoidal E_{max} models on these days were

predictive and suggested a lack of alteration of topotecan pharmacokinetics after repetitive dosing. Other studies that have adequately predicted topotecan toxicity using sigmoidal E_{max} models include the daily × 5, 30-min CI for 3 weeks study [126], the 24-h CI study [125], and the 72-h CI study in children [115]. In general, total topotecan AUC and C_{ss} were better predictors of hematological toxicity than lactone AUC and C_{ss} [49].

LSMs

LSMs have been developed to describe the pharmacokinetics/pharmacodynamics of topotecan. These allow reliable estimation of topotecan AUC and clearance values based upon a single plasma sampling time of 2 h after a 30-min intravenous infusion [124, 127].

Special populations

Topotecan exhibits significant growth inhibitory activity in pediatric xenograft models [37, 54]. Encouraged by these results, clinical trials have been conducted to evaluate the use of topotecan in children [90, 115, 123]. A dose of 1 mg/m^2/day (72-h CI) with G-CSF support has been recommended for phase II trials in children [90], with myelosuppression being the dose-limiting toxicity [90, 123]. Significantly higher levels of urinary drug recovery have been reported in children compared to adults, the mechanism for which is unclear. Prior therapy with nephrotoxic agents has been proposed to be a possible reason [115].

The safety of topotecan administration in the presence of renal and hepatic dysfunction has also been studied [84, 85, 112]. Dose adjustments have been suggested for patients with moderate renal dysfunction (creatinine clearance of 20–39 ml/min), with recommended starting doses of 0.75 mg/m^2/day for 5 days every 3 weeks [84]. Topotecan disposition and toxicity were not altered in patients with impaired hepatic function when the drug was administered at daily×5 doses of 1.5 mg/m^2/day [85].

Conclusions

CPTs are a classic example of the impact of traditional medicine on modern therapeutics. CPT and its analogues have exhibited promising anticancer activity in a variety of tumors and are undergoing extensive clinical development [30, 113, 136], with the result that 2 CPT analogues (irinotecan and topotecan) have already received Food and Drug Administration approval for use in colorectal and ovarian cancers in the USA.

Many issues regarding the clinical use of CPTs are unclear, including the significant variability in pharmacokinetics, toxicity, pharmacodynamic relationships, and mechanisms of drug interactions. Investigations are now focusing on the development of different dosing schedules and coadministration with pharmacokinetic modulators that may improve the efficacy and decrease the toxicity of CPTs. There is also considerable interest in the development of oral and extravascular formulations of CPTs, which have the advantages of more convenient administration and prolonged exposure. Recent advances in our understanding of the role of metabolic enzyme polymorphism in the disposition of irinotecan are expected to lead to more individualized dosing of irinotecan in the future. The use of CPT analogues in patients with renal and hepatic dysfunction, and in elderly and pediatric populations, needs to be more clearly delineated. Combination therapy with CPTs and other chemotherapeutic agents, such as cisplatin, as well as with radiation treatment is being investigated.

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References

1. Abigerges D, Chabot GG, Armand JP, Herait P, Gouyette A, Gandia D (1995) Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. J Clin Oncol 13:210
2. Aktipis S (1986) DNA: the replicative process and repair. In: Devlin TM (ed) Textbook of biochemistry with clinical correlations. John Wiley and Sons, New York, Chichester, Brisbane, Toronto, Singapore, p 625
3. Aräki E, Ishikawa M, Lido M, Koide T, Itabashi M, Hoshi A (1993) Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. Jpn J Cancer Res 84:697
4. Armand JP (1996) CPT-11: clinical experience in phase I studies. Sem Oncol 23:27
5. Barilero I, Gandia D, Armand JP, Mathieu-Boue A, Re M, Gouyette A, Chabot GG (1992) Simultaneous determination of the camptothecin analogue CPT-11 and its active metabolite SN-38 by high-performance liquid chromatography: application to plasma pharmacokinetic studies in cancer patients. J Chromatogr 575:275
6. Barnett AA (1996) FDA approve bark-derived drug. Lancet 347:1613
7. Betcher DL, Burnham N (1992) Topotecan. J Ped Oncol Nurs 9:31
8. Beijnen JH, Smith BR, Keijer WJ, van Gijn R, ten Bokkel Huinink WW, Vlasveld LT, Rodenhuis S, Underberg WJ (1990) High-performance liquid chromatographic analysis of the new antitumor drug SK&F 104864-A (NSC 609699) in plasma. J Pharm Biomed Anal 8:789
9. Bissery MC, Vrignaud P, Lavelle F (1996) Preclinical antitumor activity and pharmacokinetics of irinotecan (CPT-11) in tumor-bearing mice. Ann NY Acad Sci 83:173
10. Blaney SM, Balis FM, Cole DE, Craig C, Reid JM, Ames MM, Krailo M, Reaman G, Hammond D, Poplack DG (1993a) Pediatric phase I trial and pharmacokinetic study of topotecan administered as a 24-hour continuous infusion. Cancer Res 53:1032
11. Blaney SM, Cole DE, Balis FM, Godwin K, Poplack DG (1993b) Plasma and cerebrospinal fluid pharmacokinetic study of topotecan in nonhuman primates. Cancer Res 53:725
12. Blaney SM, Cole DE, Godwin K, Sung C, Poplack DG, Balis FM (1995) Intrathecal administration of topotecan in nonhuman primates. Cancer Chemother Pharmacol 36:121

13. Bosma PJ, Roy Chowdhury J, Huang, T-J, Lahiri P, Bakker C, Gantla S, Oude Elferink PJO, Van Es HHG, Lederstein M, Whitington P, Jansen PLM, Roy Chowdhury N (1992) Mechanisms of inherited deficiencies of multiple UDP-glucuronosyltransferase isoforms in two patients with Crigler-Najjar syndrome, type I. FASEB J 6:2859
14. Bosma PJ, Seppen J, Goldhoorn B, Oude Elferink RPJ, Roy Chowdhury J, Roy Chowdhury N, Jansen PLM (1994) Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. J Biol Chem 269:17960
15. Bosma PJ, Roy Chowdhury J, Bakker C, Gantla S, Boer A, Oostra BA, Lindhout D, Tytgat GNJ, Jansen PLM, Elferink RPJO, Chowdhury NR (1995) The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 333:1171
16. Bowman LC, Stewart CF, Zamboni WC, Crom WR, Luo X, Heideman R, Houghton R, Houghton PJ, Meyer WH, Pratt CB (1996) Toxicity and pharmacodynamics of oral topotecan in pediatric patients with solid tumors. Proc Am Soc Clin Oncol 15:462
17. Broom C (1996) Clinical studies of topotecan. Ann NY Acad Sci 803:264
18. Burris HA, Hanauske AR, Marshall MH, Kuhn JG, Hilsenbeck SG, von Hoff DD (1992) Activity of topotecan, a new topoisomerase I inhibitor, against human colony-forming units in vitro. J Natl Cancer Inst 84:1816
19. Burris HA III, Awada A, Kuhn JG, Eckardt JR, Cobb PW, Rinaldi DA, Fields S, Smith L, Von Hoff DD (1994) Phase I and pharmacokinetic studies of topotecan administered as a 72 or 120 h continuous infusion. Anticancer Drugs 5:394
20. Burris HA III, Gerrits CJH, Schellens JHM (1996) Oral topotecan for 10 days daily and twice daily every 3 weeks: a phase I and pharmacologic study in adults. Ann Oncol 79 (suppl 5):126
21. Chabot GG (1995) Limited sampling models for simultaneous estimation of the pharmacokinetics of irinotecan and its active metabolite SN-38. Cancer Chemother Pharmacol 36:463
22. Chabot GG (1996) Clinical pharmacology and pharmacodynamics of irinotecan. A review. Ann NY Acad Sci 83:164
23. Chabot GG, Abigerges D, Catimel G, Culine S, de Forni M, Extra JM, Mahjoubi M, Herait P, Armand JP, Bugat R (1995) Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. Ann Oncol 6:141
24. Clinical Brochure 9-Amino-20(S)-camptothecin, NSC 603071 (1992) Investigational New Drug Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, USA
25. Cole DE, Blaney SM, Balis FM (1995) Topotecan in physiologic fluids: depot of active drug in red blood cells. Proc Am Assoc Cancer Res 36:363
26. Creemers GJ, Lund B, Verweij J (1994) Topoisomerase I inhibitors: Topotecan and irinotecan. Cancer Treat Rev 20:73
27. Creemers GJ, Gerrits CJH, Eckardt JR, Schellens JHM, Burris HA, Planting AST, Rodriguez GI, Loos WJ, Hudson I, Broom C, Verweij J, Von Hoff DD (1997) Phase I and pharmacologic study of oral topotecan administered twice daily for 21 days to adult patients with solid tumors. J Clin Oncol 15:1087
28. Crigler JF, Najjar VA (1952) Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics 10:169
29. Dahut W, Harold N, Takimoto C, Allegra C, Chen A, Hamilton JM, Arbuck S, Sorensen M, Grollman F, Nakashima H, Lieberman R, Liang M, Corse W, Grem J (1996) Phase I and pharmacologic study of 9-aminocamptothecin given by 72-hour infusion in adult cancer patients J Clin Oncol 14:1236
30. Dancey J, Eisenhauer EA (1996) Current perspectives on camptothecins in cancer treatment. Br J Cancer 74:327
31. de Forni M, Bugat R, Chabot GG, Culine S, Extra JM, Gouyette A, Madelaine I, Marty ME, Mathieu-Boue A (1994) Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. Cancer Res 54:4347
32. Drengler R, Burris H, Dietz A, Eckardt J, Eckardt G, Hodges S, Kraynak M, Kuhn J, Peacock N, Rinaldi D, Rizzo J, Rodriguez G, Schaaf L, Smith L, Thurman A, Von Hoff D (1996). A phase I trial to evaluate orally administered irinotecan HCl (CPT-11) given daily×5 every 3 weeks in patients with refractory malignancies. Proc Am Assoc Clin Oncol 15:489
33. Eder JP, Rubin E, Stone R, Bryant M, Xu G, Supko J, Kinchla N, Lynch T, Hurwitz S, Rodriguez D, Shapiro C, Toppmeyer D, Grossbard M, Vosburg E, Huberman M, Schnipper L, Shulman L, Kufe DW (1996) Trials of 9-amino-20(S)-camptothecin in Boston. Ann NY Acad Sci 83:247
34. Emerson DL, Besterman JM, Roger Brown H, Evans MG, Leitner PP, Luzzio MJ, Shaffer JE, Sternbach DD, Uehling D, Vuong A (1995) In vivo antitumor activity of two new seven-substituted water-soluble camptothecin analogues. Cancer Res 55:603
35. Fagbemi S, Iyer L, Mani S, Vogelzang NJ, Cohn H, Fasanmade A, Ratain MJ (1997a) Phase I and pharmacokinetic study of irinotecan (CPT-11) administered with cyclosporine A (CSA). Proc Am Soc Clin Oncol 16:219a
36. Friedman HS, Houghton PJ, Schold SC, Keir S, Bigner DD (1994) Activity of 9-dimethylaminomethyl-10-hydroxycamptothecin against pediatric and adult central nervous system tumor xenografts. Cancer Chemother Pharmacol 34:171
37. Gilbert A, Lereboullet P (1901) La cholémie simple familiale. La Semaine Medicale 21:241
38. Giovanella BC, Stehlin JS, Wall ME, Wani MC, Nicholas AW, Liu LF, Silber R, Potmesil M (1989) DNA topoisomerase I-targeted chemotherapy of human colon cancer in xenografts. Science 246:1046
39. Gottlieb JA, Guarino AM, Call JB, Oliverio VT, Block JB (1970) Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). Cancer Chemother Rep 54:461
40. Grochow LB, Rowinsky EK, Johnson R, Ludeman S, Kaufmann SH, McCabe FL, Smith BR, Hurowitz L, DeLisa A, Donehower RC, Noe DA (1992) Pharmacokinetics and pharmacodynamics of topotecan in patients with advanced cancer. Drug Met Dispos 20:706
41. Gupta E, Lestingi TM, Mick R, Ramírez J, Vokes EE, Ratain MJ (1994) Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res 54:3723
42. Gupta E, Safa AR, Wang X, Ramírez J, Ratain MJ (1996) Pharmacokinetic modulation of irinotecan and metabolites by cyclosporin A. Cancer Res 56:1309
43. Gupta E, Ratain MJ (1997a) Camptothecin analogues: topotecan and irinotecan. In: Grochow LB, Ames M (eds) A clinician's guide to chemotherapy: pharmacokinetics and pharmacodynamics. Williams & Wilkins, Baltimore (in press)
44. Gupta E, Rosemarie M, Ramírez J, Wang X, Lestingi TM, Vokes EE, Ratain MJ (1997b) Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. J Clin Oncol 15:1502
45. Gupta E, Wang X, Ramírez J, Ratain MJ (1997c) Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. Cancer Chemother Pharmacol 39:440
46. Haas NB, La Creta FP, Walczak J, Hudes GR, Brennan JM, Ozols RF, O'Dwyer PJ (1994) Phase I/pharmacokinetic study of topotecan by 24-hour continuous infusion weekly. Cancer Res 54:1220
47. Haaz MC, Rivory LP, Riché C, Robert J (1997) Metabolism of irinotecan (CPT-11) by human hepatic microsomes: participation of cytochrome P-450 3A (CYP3A) and drug interactions. Proc Am Assoc Cancer Res 38:17
48. Hare CB, Elion GB, Houghton PJ, Houghton JA, Keir S, Marcelli SL, Bigner DD, Friedman HS (1997) Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin against pediatric and adult central nervous system tumor xenografts. Cancer Chemother Pharmacol 39:187
49. Herben VM, ten Bokkel Huinink WW, Beijnen JH (1996) Clinical pharmacokinetics of topotecan. Clin Pharmacokinet 31:85

50. Hertzberg RP, Caranfa MJ, Hecht SM (1989a) On the mechanism of topoisomerase I inhibition by camptothecin: evidence for binding to an enzymeDNA complex. Biochemistry 28:4629
51. Hertzberg RP, Caranfa MJ, Holden KG, Jakas DR, Gallagher G, Mattern MR, Mong SM, Bartus JO, Johnson RK, Kingsbury WD (1989b) Modification of the lactone ring of camptothecin: inhibition of mammalian topoisomerase I and biological activity. J Med Chem 32:715
52. Hochster H, Liebes L, Speyer J, Sorich J, Taubes B, Oratz R, Wernz J, Chachoua A, Raphael B, Vinci RZ, Blum RH (1994) Phase I trial of low-dose continuous topotecan infusion in patients with cancer: An active and well-tolerated regimen. J Clin Oncol 12:553
53. Houghton PJ, Cheshire PJ, Myers L, Houghton JA (1992) Evaluation of 9-dimethylaminomethyl-10-hydroxy camptothecin (topotecan) against xenografts derived from adult and childhood tumors. Ann Oncol 3 (suppl 1):84
54. Hsiang YH, Hertzberg R, Hecht S, Liu LF (1985) Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. J Biol Chem 260:14873
55. Hsiang YH, Lihou MG, Liu LF (1989) Arrest of replication forks by drug stabilized topoisomerase IDNA cleavable complexes as a mechanism of cell killing by camptothecin. Cancer Res 49:5077
56. Iyer L, Roy SK, Ratain MJ (1996) In vitro glucuronidation of SN-38, the active metabolite of irinotecan (CPT-11) in human liver microsomes. Proc Am Soc Clin Oncol 15:1589
57. Iyer L, King CD, Tephly T, Ratain MJ (1997a) UGT isoform 1.1 (UGT*1.1) glucuronidates SN-38, the active metabolite of irinotecan. Proc Am Soc Clin Oncol 16:201a
58. Iyer L, Whitington PF, Roy SK, Ratain MJ (1997b) Genetic basis for the glucuronidation of SN-38: role of UGT*1 isoform. Clin Pharmacol Ther 61:164
59. Iyer L, King CD, Whitington PF, Green MD, Roy SK, Tephly TR, Coffman BL, Ratain MJ (1997c) Genetic predisposition to the metabolism of irinotecan (CPT-11): role of UGT isoform 1A1 (UGT1A1) in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest (in press)
60. Jones SF, Burris HA (1996) Topoisomerase I inhibitors: topotecan and irinotecan. Cancer Pract 4:51
61. Kaneda N, Nagata H, Furuta T, Yokokura T (1990a) Metabolism and pharmacokinetics of camptothecin analogue CPT-11 in the mouse. Cancer Res 50:1715
62. Kaneda N, Yokokura T (1990b) Nonlinear pharmacokinetics of CPT-11 in rats. Cancer Res 50:1721
63. Kantarjian HM, Beran M, Ellis A, Zwelling L, O'Brien S, Cazenave L, Koller C, Rios MB, Plunkett W, Keating MJ, Estey EH (1993) Phase I study of topotecan, a new topoisomerase I inhibitor, in patients with refractory or relapsed acute leukemia. Blood 81:1146
64. Kawato Y, Aonuma M, Matsumoto K, Sato K (1991a) Production of SN-38, a main metabolite of the camptothecin derivative CPT-11, and its species and tissue specificities. Yakubutsu Dotai 6:899
65. Kawato Y, Nagata T, Furuta T, Yokokura T (1991b) Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the anti-tumor effect of CPT-11. Cancer Res 51:4187
66. Kawato Y, Sekiguchi M, Akahane K, Tsutomi Y, Hirota Y, Kuga H, Suzuki W, Hakusui H, Sato K (1993) Inhibitory activity of camptothecin derivatives against acetylcholinesterase in dogs and their binding activity to acetylcholine receptors in rats. J Pharm Pharmacol 45:444
67. Kuhn J, Rizzo J, Eckardt J (1995) Phase I bioavailability study of oral topotecan. Proc Am Soc Clin Oncol 14:1538
68. Kunimoto T, Nitta K, Tanaka T, Uehara N, Baba H, Takeuchi M, Yokokura T, Sawada S, Miyasaka T, Mutai M (1987) Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. Cancer Res 47:5944
69. Li LH, Fraser TJ, Bhuyan OBK (1972) Action of camptothecin on mammalian cells in culture. Cancer Res 32:2643
70. Liang MD, Dahut W, Quin MF, Harold N, Arbuck SG, Chen A, Hamilton JM, Sorensen JM, Allegra CJ, Grem JL, Takimoto CH (1996) Preclinical and clinical studies of a new colloidal dispersion formulation of 9-Aminocamptothecin. Proc Am Assoc Cancer Res 37:432
71. Liehr JG, Ahmed AE, Giovanella B (1996) Pharmacokinetics of camptothecins administered orally. Ann NY Acad Sci 83:157
72. Liu LF, Duann P, Li C, D'arpa P, Wu J (1996). Mechanism of action of camptothecin. Ann NY Acad Sci 83:44
73. Mani S, Iyer L, Janisch L, Wang X, Fleming GF, Schilsky RL, Ratain MJ (1997) Phase I clinical and pharmacokinetic study of oral 9-aminocamptothecin (NSC-603071). Proc Am Soc Clin Oncol 16:201a
74. McCabe FL, Johnson RK (1994) Comparative activity of oral and parenteral topotecan in murine tumor models: Efficacy of oral topotecan. Cancer Invest 12:308
75. McLeod HL, Douglas F, Oates M, Symonds RP, Prakash D, vander-Zee AG, Kaye SB, Brown R, Keith WN (1994) Topoisomerase I and II activity in human breast, cervix, lung and colon cancer. Int J Cancer 59:607
76. Mick R, Gupta E, Vokes EE, Ratain MJ (1996) Limited-sampling models for irinotecan pharmacokinetics-pharmacodynamics: prediction of biliary index and intestinal toxicity. J Clin Oncol 14:2012
77. Minami H, Mick R, Vokes EE, Ratain MJ (1996) Pharmacodynamic models for leukopenia and thrombocytopenia of 9-aminocamptothecin (9-AC). Proc Am Soc Clin Oncol 15:179
78. Moertel CG, Schutt AJ, Reitemeier RJ, RG Hahn (1972) Phase II study of camptothecin (NSC-100880) in the treatment of advanced gastrointestinal cancer. Cancer Chemother Rep 56:95
79. Monaghan G, Ryan M, Seddon R, Hume R, Burchell B (1996) Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet 347:578
80. Moore A, Imondi A, L'Heureux D (1997) Preclinical evaluation of three dosage schedules of 9-aminocamptothecin (9AC) for the treatment of spontaneous lymphoma in dogs. Proc Am Assoc Cancer Res 38:75
81. Muggia FM, Creaven PJ, Hansen HH, Cohen MH, Selawry OS (1972) Phase I clinical trial of weekly and daily treatment with camptothecin (NSC-100880): correlation with preclinical studies. Cancer Chemother Rep 56:515
82. Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Niitani H, Taguchi T (1991) Phase I study of weekly intravenous infusions of CPT-11, and new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. J Natl Cancer Inst 83:1164
83. Ohe Y, Sasaki Y, Shinkai T, Eguchi K, Tamura T, Kojima A, Kunikane H, Okamoto H, Karato A, Ohmatsu H, Kanzawa F, Saijo N (1992) Phase I study and pharmacokinetics of CPT-11 with 5-day continuous infusion. J Natl Cancer Inst 84:972
84. O'Reilly S, Rowinsky E, Slichenmyer W, Donehower RC, Forastiere A, Ettinger D, Chen TL, Sartorius S, Grochow LB (1996a) Phase I and pharmacologic study of topotecan in patients with impaired renal function. J Clin Oncol 14:3062
85. O'Reilly S, Rowinsky E, Slichenmyer W, Donehower RC, Forastiere A, Ettinger D, Chen TL, Sartorius S, Bowling K, Smith J, Brubaker A, Lubejko B, Ignacio V, Grochow LB (1996b) Phase I and pharmacologic studies of topotecan in patients with impaired hepatic function. J Natl Cancer Inst 88:817
86. Pantazis P, Hinz HR, Mendoza JT, Kozielski AJ, Williams LJ Jr, Stehlin JS Jr, Giovanella BC (1992) Complete inhibition of growth followed by death of human malignant melanoma cells in vitro and regression of human melanoma xenografts in immunodeficient mice induced by camptothecins. Cancer Res 52:3980
87. Pastori A, Farao M, Geroni C, Porro MG, Grandi M (1997) Antitumor activity of 9-aminocamptothecin (9-AC) by s.c. and oral route. Proc Am Assoc Cancer Res 38:18
88. Potmesil M, Giovanella BC, Wall ME, Liu LF, Silber R, Stehlin JS, Wani MC, Hochster H (1993) Preclinical and clinical development of DNA topoisomerase I inhibitors in the United States. In:

Andoh T, Ikeda H, Oguro M (eds) Molecular biology of topoi somerases and its application to chemotherapy. CRC, Nagoya, p 301
89. Potmesil M, Arbuck SG, Takimoto CH, Liebes L, Hochster H (1996) 9-aminocamptothecin and beyond, preclinical and clinical studies. Ann NY Acad Sci 83:231
90. Pratt CB, Stewart C, Santana VM, Bowman L, Furman W, Ochs J, Marina N, Kuttesch JF, Heideman R, Sandlund JT, Avery L, Meyer WH (1994) Phase I study of topotecan for pediatric patients with malignant solid tumors. J Clin Oncol 12:539
91. Pratesi G, Tortoreto M, Corti C, Giardini R, Zunino F (1995) Successful local regional therapy with topotecan of intraperitoneally growing human ovarian carcinoma xenografts. Br J Cancer 71:525
92. Ratain MJ, Mick R, Gupta E, Lestingi TM, Schilsky RL, Vokes EE (1996) Prospective evaluation of the effect of race and gender on irinotecan (CPT-11) pharmacokinetics (PK) and intestinal toxicity. Proc Am Soc Clin Oncol 15:472
93. Recondo G, Abbruzzese J, Newman B (1991) A phase I trial of topotecan administered by a 24-h infusion. Proc Am Assoc Cancer Res 32:206
94. Rivory LP, Robert J (1994) Reversed-phase high-performance liquid chromatographic method for the simultaneous quantitation of the carboxylate and lactone forms of the camptothecin derivative irinotecan, CPT-11, and its metabolite SN-38 in plasma. J Chromatogr 661:133
95. Rivory LP, Robert J (1995) Identification and kinetics of a beta-glucuronide metabolite of SN-38 in human plasma after administration of the camptothecin derivative, irinotecan. Cancer Chemother Pharmacol 36:176
96. Rivory LP, Riou JF, Haaz MC, Sable S, Vuilhourgne M, Commercon A, Pond SM, Robert J (1996) Identification and properties of a major plasma metabolite of irinotecan (CPT-11) isolated from the plasma of patients. Cancer Res 56:3689
97. Rothenberg ML (1996a) CPT-11: an original spectrum of clinical activity. Semin Oncol 23:21
98. Rothenberg ML (1996b) The current status of irinotecan (CPT-11) in the United States. Ann NY Acad Sci 83:272
99. Rothenberg ML, Kuhn JG, Burris HA III, Nelson J, Eckardt JR, Tristan-Morales M, Hilsenbeck SG, Weiss GR, Smith LS, Rodrigues GI, Rock MK, Von Hoff DD (1993) Phase I and pharmacokinetic trial of weekly CPT-11. J Clin Oncol 11:2194
100. Rougier P, Bugat R (1996) CPT-11 in the treatment of colorectal cancer: clinical efficacy and safety profile. Semin Oncol 23:34
101. Rowinsky EK, Gorchow LB, Hendricks CB, Ettinger DS, Forastiere AA, Hurowitz LA, McGuire WP, Sartorius SE, Lubejko BG, Kaufmann SH, Donehower RC (1992) Phase I and pharmacologic study of topotecan: A novel topoisomerase I inhibitor. J Clin Oncol 10:647
102. Rowinsky EK, Grochow LB, Ettinger DS (1994) Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks. Cancer Res 54:427
103. Rubin E, Wood V, Bharti A, Trites D, Lynch C, Hurwitz S, Bartel S, Levy S, Rosowsky A, Toppmeyer D, Kufe D (1995) A phase I and pharmacokinetic study of a new camptothecin derivative, 9-aminocamptothecin. Clin Cancer Res 1:269
104. Saltz L, Sirott M, Young C, Tong DN, Tzy-Jyun Y, Tao Y, Tochanowski B, Wright P, Barbosa K, Toomasi F, Kelsen D (1993) Phase I clinical and pharmacology study of topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor. J Natl Cancer Inst 85:1499
105. Sasaki Y, Hakusui H, Mizuno S, Morita M, Miya T, Eguchi K, Shinkai T, Tamura T, Ohe Y, Saijo N (1995a) A pharmacokinetic and pharmacodynamic analysis of CPT-11 and its active metabolite SN-38. Jpn J Cancer Res 86:101
106. Sasaki Y, Yoshida Y, Sudoh K, Hasusui H, Fujii H, Ohtsu T, Wakita H, Igarashi T, Itoh K (1995b) Pharmacological correlation between total drug concentration and lactones of CPT-11 and SN-38 in patients treated with CPT-11. Cancer Res 86:111
107. Sasaki Y, Mizuno S, Fujii H, Ohtsu T, Wakita H, Igarashi T, Itoh K, Sekine I, Miyata Y, Saijo N (1995c) A limited sampling model for estimating pharmacokinetics of CPT-11 and its active metabolite SN-38. Jpn J Cancer Res 86:117
108. Schaaf L, Ichhpurani N, Elfring G, Wolf D, Rothenberg M, Von Hoff D (1997) Influence of age on the pharmacokinetics of irinotecan (CPT-11) & its metabolites, SN-38 and SN-38 glucuronide (SN-38G), in patients with previously treated colorectal cancer. Proc Am Soc Clin Oncol 16:202a
109. Schellens JHM, Eckardt JR, Creemers GJ, Loos WJ, McDonald M, Broom C, Davies BE, Verweij J, van Hoff DD (1995) Pharmacokinetics, clinical pharmacodynamics and safety of chronic oral topotecan in a phase I study. Proc Am Soc Clin Oncol 14:457
110. Schellens JHM, Creemers GJ, Beijnen JH, Rosing H, de Boer-Dennert M, McDonald M, Davies B, Verwij J (1996) Bioavailability and pharmacokinetics of oral topotecan: A new topoisomerase I inhibitor. Br J Cancer 73:1268
111. Shimada Y, Rothenberg M, Hilsenbeck SG, Burris HA, Degen D, Von Hoff DD (1994) Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumor colony-forming units. Anticancer Drugs 5: 202
112. Slichenmyer WJ, Rowinsky EK, Grochow LB, Kaufmann SH, Donehower RC (1994) Camptothecin analogues: studies from the Johns Hopkins Oncology Center. Cancer Chemother Pharmacol 34:S53
113. Slichenmyer WJ, Donehower RC (1995) Recent clinical advances with camptothecin analogues. Cancer Treat Res 78:29
114. Sparreboom A, Stoter G, Loos WJ, Nooter K, Punt CJA, Calajori E, Verweij J (1997) Oral bioavailability of 9-aminocamptothecin in adult patients with solid tumors. Proc Am Assoc Cancer Res 38:75
115. Stewart CF, Baker SD, Heideman RL, Jones D, Crom WR, Pratt CB (1994) Clinical pharmacodynamics of continuous infusion topotecan in children: systemic exposure predicts hematologic toxicity. J Clin Oncol 12:1946
116. Stewart CF, Zamboni WC, Crom WR, Houghton PJ (1997) Disposition of irinotecan and SN-38 following oral and intravenous irinotecan dosing in mice. Cancer Chemother Pharmacol 40:259
117. Supko JG, Malspeis L (1992). Liquid chromatographic analysis of 9-aminocamptothecin in plasma monitored by fluorescence induced upon postcolumn acidification. J Liq Chromatogr 15:3261
118. Takasuna K, Hagiwara T, Hirohshi M, Kato M, Nomura M, Nagai E, Yokoi T, Kamataki T (1996) Involvement of β-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (CPT-11) in rats. Cancer Res 56:3752
119. Takimoto CH, Klecker RW, Dahut WL, Yee LK, Strong JM, Allegra CJ, Grem JL (1994) Analysis of the active lactone form of 9-aminocamptothecin in plasma using solid-phase extration and high-performance liquid chromatography. J Chromatogr 655:97
120. Takimoto CH, Dahut W, Harold N, Nakashima H, Lieberman R, Liang MD, Arbuck SG, Chen AP, Hamilton JM, Cantilena LR, Allegra CJ, Grem JL (1996) Clinical pharmacology of 9-aminocamptothecin. Ann NY Acad Sci 83:324
121. Takimoto CH, Dahut W, Marino MT, Nakashima H, Liang MD, Harold N, Leiberman R, Arbuck S, Band RA, Chen AP, Hamilton JM, Cantilena LR, Allegra CJ, Grem JL (1997) Pharmacodynamics and pharmacokinetics of a 72-hour infusion of 9-aminocamptothecin in adult cancer patients. J Clin Oncol 15:1492
122. Tsuji T, Kaneda N, Kado K, Yokokura T, Yoshimoto T, Tsuru D (1991) CPT-11 converting enzyme from rat serum: purification and some properties. J Pharmacobiodyn 14:341
123. Tubergen DG, Stewart CF, Pratt CB, Zamboni WC, Winick N, Santana VM, Dryer ZA, Kurtzberg J, Bell B, Grier H, Vietti TJ (1996) Phase I trial and pharmacokinetic (PK) and pharmacodynamics (PD) study of topotecan using a five-day course in children with refractory solid tumors: a Pediatric Oncology Group study. J Pediatr Hematol Oncol 18:352

124. van Warmerdam LJC, Verweij J, Rosing, Schellens JHM, Maes RAA, Beijnen JH (1994) Limited sampling models for topotecan pharmacokinetics. Ann Oncol 5:259
125. van Warmerdam LJC, Bokkel Huinink WW, Rodenhuis S, Koier I, Davies BE, Rosing H, Maes RAA, Beijnen JH (1995a) Phase I clinical and pharmacokinetic study of topotecan administered by a 24-hour continuous infusion. J Clin Oncol 13: 1768
126. van Warmerdam LJC, Verweij J, Schellens JHM, Rosing H, Davies BE, de Boer-Dennert M, Maes RAA, Beijinen JH (1995b) Pharmacokinetics and pharmacodynamics of topotecan administered daily for 5 days every 3 weeks. Cancer Chemother Pharamacol 35:237
127. van Warmerdam LJC, Creemers GJ, Rodenhuis S, Rosing H, de Boer-Dennert M, Schellens JHM, Huinink WWB, Davies BE, Maes RAA, Verweij J, Beijnen JH (1996) Pharmacokinetics and pharmacodynamics of topotecan given on a daily-time-five schedule in phase II clinical trials using a limited-sampling procedure. Cancer Chemother Pharmacol 38:254
128. Vassal G, Terrier-Lacombe MJ, Bissery MC, Venuat AM, Gyergyay F, Benard J, Morizet J, Boland I, Ardouin P, Bressac-de-Paillerets B, Gouyette A (1996) Therapeutic acitivity of CPT-11, a DNA-topoisomerase I inhibitor, against peripheral primitive neuroectodermal tumour and neruoblastoma. Br J Cancer 74:537
129. Verweij J, Lund B, Bijnen J, Planting A, de Boer-Dennert M, Koier I, Rosing H, Hansen H (1993) Phase I and pharmacokinetics study of topotecan, a new topoisomerase I inhibitor. Ann Oncol 4:673
130. Von Hoff DD, Burris HA III, Eckardt J, Rothenberg M, Fields SM, Chen SF, Kuhn JG (1994) Preclinical and phase I trials of topoisomerase I inhibitors. Cancer Chemother Pharmacol 34:S41
131. Wall ME, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA (1966) Plant antitumor agents: I. The isolation and structure of camptothecin, a novel alkaloidal leukemia tumor inhibitor from Camptotheca acuminata. J Am Chem Soc 88:3888
132. Wall JG, Burris HA III, Von Hoff DD, Rodriguez G, Kneuper-Hall R, Shaffer D, O'Rourke T, Brown T, Weiss G, Clark G, McVea S, Brown J, Johnson R, Friedman C, Smith B, Mann WS, Kuhn J (1992) A phase I clinical and pharmacokinetic study of the topoisomerase I inhibitor topotecan (SK&F 104864) given as an intravenous bolus every 21 days. Anticancer Drugs 3:337
133. Wasserman E, Myara A, Paumier D, Herait P, Awad L, Misset JL, Cvitkovic E (1997) Baseline bilirubin (bil) and its transient early increase predicts likelihood of severe neutropenia and diarrhea in CPT-11-based chemotherapy. Proc Am Soc Clin Oncol 16:219a
134. Wani MC, Ronman PE, Lindley JT, Wall ME (1980) Plant antitumor agents. 18. Synthesis and biological activity of camptothecin analogues. J Med Chem 23:554
135. Wani MC, Nicholas AW, Wall ME (1986) Plant antitumor agents. 23. Synthesis and biological activity of camptothecin analogues. J Med Chem 29:2358
136. Willson JKV (1996) Topoisomerase-I inhibitors in the management of colon cancer. Ann NY Acad Sci 803:256
137. Yamamoto N, Tamura T, Nishiwaki Y, Kawakami Y, Abe S, Nakabayashi T, Suzuki S, Matsuda T, Hayashi I, Takahashi T, Saijo N (1997) Limited sampling model for the area under the concentration versus time curve of irinotecan and its application to a multicentric phase II trial. Clin Cancer Res 3:1087