REVIEW ARTICLE

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Camptothecin and Podophyllotoxin Derivatives

Inhibitors of Topoisomerase I and II – Mechanisms of Action, Pharmacokinetics and Toxicity Profile

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Contents

Abstract

Camptothecins represent an established class of effective agents that selectively target topoisomerase I by trapping the catalytic intermediate of the topoisomerase I-DNA reaction, the cleavage complex. The water-soluble salt camptothecin-sodium – introduced in early trials in the 1960s – was highly toxic in animals, whereas the semisynthetic derivatives irinotecan and topotecan did not cause haemorrhagic cystitis because of their higher physicochemical stability and solubility at lower pH values. Myelosuppression, neutropenia and, to a lesser extent, thrombocytopenia are dose-limiting toxic effects of topotecan. In contrast

to the structurally-related topotecan, irinotecan is a prodrug which has to be converted to SN-38, its active form. SN-38 is inactivated by conjugation, thus patients with Gilbert's syndrome and other forms of genetic glucuronidation deficiency are at an increased risk of irinotecan-induced adverse effects, such as neutropenia and diarrhoea.

The cytotoxic mechanism of podophyllotoxin is the inhibition of topoisomerase II. Common adverse effects of etoposide include dose-limiting myelosuppression. Hypersensitivity reactions are more common with etoposide and teniposide than with etoposide phosphate because the formulations of the former contain sensitising solubilisers. Leukopenia and thrombocytopenia occur in 65% and 80%, respectively, of patients after administration of conventional doses of teniposide. Anorexia, vomiting and diarrhoea are generally of mild severity after administration of conventional doses of topoisomerase II inhibitors. Clinical pharmacokinetic studies have revealed substantial interindividual variabilities regarding the area under the concentration-time curve values and steady-state concentrations for all drugs reviewed in this article. Irinotecan, etoposide and teniposide are degraded via complex metabolic pathways. In contrast, topotecan primarily undergoes renal excretion. Regarding etoposide and teniposide, the extent of catechol formation over time during drug metabolism may be associated with a higher risk for secondary malignancies.

Inhibitors of topoisomerase I and II are commonly used anticancer drugs that are active cytotoxic agents in a variety of hematological cancers and solid tumours. A number of new compounds have been developed recently. The topoisomerases have functions in DNA-replication, chromosome condensation and chromosome segregation, and are highly conserved enzymes essential for the survival of eukaryotic cells. These drugs are part of several treatment regimens approved for the treatment of different cancers (e.g. ovarian, lung, colorectal and testicular carcinoma, non-Hodgkin's lymphoma and CNS tumours). Topoisomerase I and II inhibitors differ in their pharmacological properties, and pharmacokinetic and toxicity profiles. Clinical pharmacokinetic studies have revealed substantial variability regarding the area under the concentration-time curve (AUC) and steady state concentrations for the topoisomerase I and II inhibitors.[1-5] Whereas irinotecan, etoposide and teniposide move through complex metabolic pathways during drug degradation, topotecan is eliminated via renal excretion without major degradation. In the case of irinotecan, plasma concentrations of the active metabolite SN-38 cannot predict the overall rate of drug-associated adverse effects, based on SN-38-associated activity in the gut lumen.[4] The camptothecin derivatives, topotecan and irinotecan, interact with the enzyme topoisomerase I, whereas the podophyllotoxin derivatives, etoposide and teniposide, target the enzyme topoisomerase II, resulting in different DNA disorders.[1] Topoisomerase I modulates the topological structure of DNA by inducing transient DNA breaks. These single-strand breaks help to remove excessive positive and negative DNA supercoils, which arise during DNA replication and transcription. The interaction between the camptothecins and the enzyme results in the formation of a topoisomerase I DNA complex.[2]

In contrast to topoisomerase II, cellular levels of topoisomerase I are relatively independent of the cell cycle phase in normal tissues. Thus, topoisomerase I activity is only slightly increased during conditions of cellular proliferation in cells and tissues. However, higher constitutive activities of this enzyme can be detected in several tumour tissues (e.g. adenocarcinoma of the colon and rectum) compared with healthy tissues.[6]

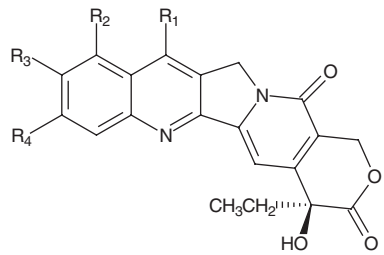
This review summarises the drug development, pharmacological, pharmacokinetic, therapeutic and safety aspects of topoisomerase I and II inhibitors, in particular the camptothecins, irinotecan, exatecan

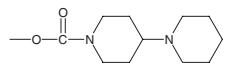
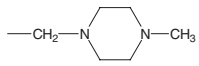
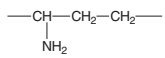
and topotecan, as well as the podophyllotoxins, etoposide and teniposide, and describes the possible supportive management and clinically relevant strategies to avoid toxicity by taking into account both clinical and pharmacological perspectives. Therefore, we searched the published literature on MEDLINE from January 1990 to December 2004, including only English-language articles. Searches were conducted using the keywords: 'human clinical trials', 'camptothecin', 'podophyllotoxin', 'topoisomerase I inhibitor', 'topoisomerase II inhibitor', 'pharmacology', 'pharmacokinetics', 'toxicity', 'side effects', 'irinotecan', 'topotecan', 'exatecan', 'teniposide', 'etoposide' and 'etoposide phosphate'. Additionally, case reports were selected for evaluation and an extensive search of bibliographies from identified articles was performed. The literature was assessed for quality, methodology and outcome information.

1. Camptothecins

1.1 Mechanism of Action

Camptothecins (figure 1) were originally isolated from the wood, bark and fruit of the oriental tree, *Camptotheca acuminata* ('tree of joy'). Why the tree produces these highly toxic alkaloids is not known, but the most likely reason is that the toxins are part of a survival strategy to help combat herbivores. Among a large number of isolated plant con-



Compound	Molecular weight	R_1	R_2	R_3	R_3
Camptothecin	348.36	–H	–H	–H	–H
Topotecan	421.46[a]	–H	$-CH_2N(CH_3)_2$	–OH	–H
Irinotecan	586.69[a]	$-CH_2CH_3$	–H		–H
SN-38	392.42	$-CH_2CH_3$	–H	–OH	–H
9-Aminocamptothecin	363.38	–H	$-NH_2$	–H	–H
9-Nitrocamtothecin	393.36	–H	$-NO_2$	–H	–H
Lurtotecan (GI-147211)	518.57[a]		–H	$-OCH_2CH_2O-$	
Exatecan	435.46[a]			$-CH_3$	–F
Karenitecin	448.60	–H	$-CH_2CH_2Si(CH_3)_3$	–H	–H

a Free base

Fig. 1. Chemical structures of camptothecins (reproduced from Garcia-Carbonero et al.,[4] with permission).

Table I. A comparison of topoisomerase I inhibitors: topotecan and irinotecan

Parameter	Topotecan	Irinotecan
Approved indication	Second-line treatment of advanced ovarian cancer and SCLC	Metastatic colorectal cancer
Dosage	1.5 mg/m^2 IV d1–5, q3w Under investigation: 4 mg/m^2 IV q1w (ovarian cancer)	350 mg/m^2 IV, q3w 50–150 mg/m^2 IV, q1w Under investigation: e.g. 200–250 mg/m^2 q2w; 80–125 mg/m^2 q1w
Clinical pharmacokinetics	Predominantly renal excretion with large amounts excreted as the parent drug	Prodrug that has to be converted to SN-38. Further metabolism includes SN-38 glucuronide, APC and NPC formation. Biliary excretion is greater than renal excretion.
	$t_{1/2}$ β: 2–3h (approximately 3h)	$t_{1/2\beta}$: approximately 14h

APC = 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin; **IV** = intravenous; **NPC =** 7-ethyl-10-[-(1-piperidino)-1-amino]-carbonyloxycamptothecin; **qxw** = every 'x' weeks; **SCLC** = small-cell lung cancer; $\mathbf{t}_{1/2\beta}$ = terminal elimination half-life.

stituents, the naturally occurring alkaloid camptothecin (NSC94600) was identified as a highly potent inhibitor of topoisomerase I, which is overexpressed in many cancer cells. The water-soluble salt camptothecin-sodium, which was introduced in early preclinical trials in the 1960s, was highly toxic in animals.[2] Hemorrhagic cystitis, leukopenia and thrombocytopenia were among the dose-limiting adverse effects of this agent. In addition, sterile haemorrhagic cystitis, myelosuppression, and gastrointestinal toxicity were common in patients during phase I studies.[2] Further clinical trials with camptothecin-sodium were, therefore, discontinued in the 1970s.[2] However, the semisynthetic derivatives irinotecan and topotecan (figure 1) are highly active in several malignancies and, because of their higher physicochemical stability and solubility at lower pH values, do not cause haemorrhagic cystitis.[1] However, the drugs differ from each other in their approved therapeutic indications, recommended doses, toxicity profiles and clinical pharmacokinetics (table I).

Both irinotecan and topotecan contain a lactone moiety within their chemical structure (figure 2), which can be hydrolysed non-enzymatically, resulting in the open-ring form.[7] Under acidic conditions, the equilibrium between the biologically active lactone and the less active carboxylate form is generally shifted to the lactone form, whereas at physiological or higher pH values the lactone form becomes unstable because hydrolysis to the open form is favoured.[7] In addition, the affinity of the carboxylate form for human serum albumin is estimated to be about 100-fold higher than that of the lactone form. As a consequence, >95% of the irinotecan dose is bound to serum albumin as a transiently inactive drug when irinotecan is given intravenously.[8] Novel camptothecin derivatives, such as exatecan or lurtotecan (GI-147211), are more resistant to rapid hydrolysis due to their structural modifications (e.g. by the removal of the 20-OH group [figure 2]).[4]

1.2 Topotecan

Topotecan, administered as an intravenous (IV) infusion of 1.5 mg/m^2 for 5 consecutive days of a 21-day cycle, has been approved for the second-line treatment of advanced ovarian and small-cell lung

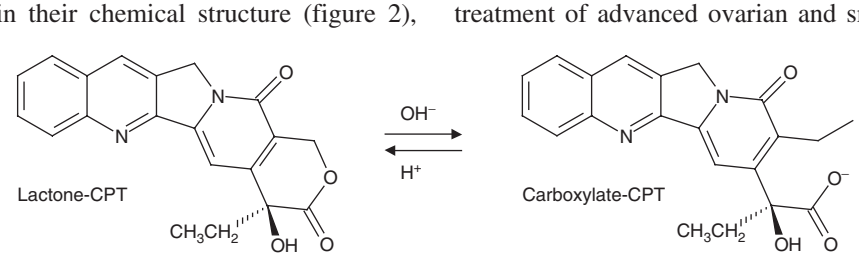


Fig. 2. The carboxylate-lactone equilibrium of camptothecin (CPT) [reproduced from Loos et al.,[9] with permission].

cancer (SCLC) in several countries.[10] Preliminary data indicate that a dosage of 4 mg/m^2/week may be associated with improved activity and reduced toxicity in patients with recurrent or persistent epithelial ovarian carcinoma.[11]

1.2.1 Clinical Pharmacokinetics

After IV administration of conventional dosages (e.g. 1.5 mg/m^2/day as a 30-minute infusion, on 5 consecutive days every 3 weeks), the half-life of topotecan is, on average, 3.2 hours (2.3–4.3 hours).[10] The ratio of the AUC of the lactone to that of total topotecan appears to be relatively constant after IV administration, and averages about 0.20 over several hours, which means that only 20% of the total drug concentration in plasma represent the closed-ring active lactone form.[10] The volume of distribution during steady-state conditions has been estimated to be 25–75 L/m^2, indicating extensive tissue binding.[10,12] Red blood cells appear to act as a type of depot for topotecan (the lactone form), with steady-state concentrations that are almost 1.7-fold higher than those obtained in the plasma.[13]

Following IV administration, topotecan is primarily excreted unchanged in the urine. Approximately 40% of the total dose (range 26–80%) can be recovered in the urine within 24 hours after the start of a 30-minute infusion, whereas up to 18% of dose can be recovered in the faeces. Urinary excretion of the carboxylate form is predominant when the urinary pH approximates a value of 6.9. Lower pH values may favour the lactone form. Despite these high urinary concentrations, topotecan itself does not cause urinary toxicity because of its high water solubility.[10,12] Dose modification is warranted in patients with impaired renal function.[14] Reduced dosages of 0.75 mg/m^2/day and 0.5 mg/m^2/day have been recommended in patients with reduced creatinine clearance (20–40 mL/min) who are either untreated or have been extensively pretreated, respectively.[15] It has also been suggested that dosage adjustment may even be required if the creatinine clearance ranges from 40–60 mL/min. In those patients, the recommended starting dose should be 1.2 mg/m^2/day IV on 5 consecutive days, in order to reduce the risk for severe myelosuppression.[16] In general, topotecan should not be given to patients with severe renal insufficiency (e.g. creatinine clearance <20 mL/min) until further data are available. In contrast, patients with impaired liver function and hyperbilirubinaemia do not appear to require topotecan dose modification. Preliminary study results indicate that topotecan is haemodialysable, when needed.[17]

Hepatic metabolism of topotecan, mediated by cytochrome P450 (CYP) isoenzymes, is of minor quantitative importance. Metabolic pathways include N-dealkylation (resulting in N-demethyltopotecan) and glucuronidation.[10]

The plasma protein binding of topotecan appears to be low (7–35%).[10] In contrast to many other anticancer drugs, topotecan is able to pass through the blood-brain-barrier.[18] More than 30% of the plasma concentration of topotecan can be recovered in the cerebrospinal fluid (CSF).[18] Nevertheless, intrathecal drug administration (e.g. 0.4mg absolute dose) has been suggested to be advantageous when high concentrations in the CSF are warranted, in order to reduce the systemic toxicity. However, experience with this is thus far is based on preclinical study results and case reports.[19,20]

1.2.2 Tolerability Profile

Myelosuppression, neutropenia and, to a lesser extent, thrombocytopenia are dose-limiting adverse effects of topotecan. Reversible non-cumulative neutropenia usually occurs between days 8 and 15 after a dosage of 1.5 mg/m^2 IV on 5 consecutive days. The nadir of the neutrophil count usually occurs on day 11, with recovery on day 21.[21] Neutropenia, with cell counts $<1.5 \times 10^9$/L (grade 2) and $<0.5 \times 10^9$/L (grade 4), is observed in 70–97% of patients. In addition, 4–33% of patients treated with conventional doses of topotecan develop neutropenic fever during treatment cycles.[21]

Thrombocytopenia, with platelet counts $<50 \times 10^9$/L (grade 3) and $<25 \times 10^9$/L (grade 4), occurs in 25–77% of patients, with a nadir on day 15 and recovery on day 21.[21] Platelet transfusions are needed in 4–27% of patients.[21] Anaemia, defined as a fall in haemoglobin levels to below 8 g/dL (grade 3) or 6.5 g/dL (grade 4), has been reported in 21–41% of patients during treatment cycles.[21] As a consequence, red blood cell transfusions may be required in approximately 25% of treated patients.[21] More extensive myelosuppression is ob-

Table II. Inhibitors and inducers of cytochrome P450 (CYP) 3A4-mediated biotransformation of topoisomerase I and II inhibitors

Interaction	Effect	Interacting agents
CYP3A4 inhibition	Increased topoisomerase inhibitor concentrations in the plasma	Amiodarone, cisapride, clarithromycin, erythromycin, ciclosporin, tacrolimus, delavirdine, ritonavir, fluconazole, voriconazole, itraconazole, ketoconazole, fluoxetine, grapefruit juice, nefazodone, terfenadine, verapamil, quinupristin/dalfopristin
CYP3A4 induction	Decreased topoisomerase inhibitor concentration in the plasma	Barbiturates, carbamazepine, oxcarbazepine, griseofulvin, nafcillin, phenytoin, primidone, rifabutin, rifampicin (rifampin), St John's wort, troglitazone

served in patients who have been extensively pretreated with cytotoxic drugs. The extent of myelosuppression correlates significantly with both the total topotecan AUC and the topotecan lactone AUC.[10] When granulocyte colony-stimulating factor (G-CSF) is given as prophylaxis against neutropenia, thrombocytopenia becomes the dose-limiting myelotoxic effect.[21] In contrast to the structurally related irinotecan, gastrointestinal discomfort with topotecan is generally of mild severity.

1.2.3 Important Drug Interactions

Administration of cisplatin before topotecan has been shown to result in a sequence-dependent effect on the disposition of topotecan.[22] Cisplatin-related acute changes in the glomerular filtration rate can temporarily alter topotecan clearance, with more severe myelosuppression as a consequence. Nevertheless, this sequence has sometimes been recommended in clinical trials, based on a potential exaggeration of the antineoplastic activity and the possibility of the use of G-CSF support to circumvent the adverse effect of neutropenia. However, severe thrombocytopenia may also occur, which limits the use of this treatment strategy.[23-25] There is some evidence that potent inhibitors or inducers of CYP3A4 may be able to alter the clearance of topotecan; however, whether such interactions result in clinically relevant consequences has not yet been elucidated (table II).[10]

1.2.4 Oral Formulation

In addition, an oral formulation of topotecan is undergoing clinical development.[26-28] Administration schedules of oral topotecan 2.3 mg/m^2/day for 5 days revealed similar efficacy results to topotecan 1.5 mg/m/day IV for 5 days in patients with chemosensitve SCLC,[26] whereas the IV schedule was suggested to be favourable with regard to survival in patients with relapsed epithelial ovarian cancer.[28] In general, oral topotecan appears as if it will be a convenient and well tolerated regimen for the treatment of defined solid tumours in the near future.[26-28]

1.3 Irinotecan

Irinotecan has been approved for the first- and second-line treatment of advanced colorectal cancer, and has also been shown to be active in gastric cancer, non-small-cell lung cancer (NSCLC) and SCLC. Conventional dosages include 350 mg/m^2 IV every 3 weeks, 200–250 mg/m^2 IV every 2 weeks and 80–125 mg/m^2 IV weekly (see table I), whether given as a single agent or in combination (e.g. with 5-fluorouracil and folinic acid weekly). In contrast to the structurally related topotecan, irinotecan is a prodrug that needs bioactivation to SN-38 to become active.[5,29,30]

1.3.1 Clinical Pharmacokinetics

Following IV administration, the bulky piperidino moiety at the C10 position of irinotecan is rapidly removed by carboxylesterases (CES). Of the three isoenzymes, CES2 plays the pivotal role in metabolism, followed by CES1A1 and CES3.[31]

SN-38 is approximately 1000-fold more potent than its parent compound, irinotecan. There is a pH- and protein-dependent equilibrium between the active lactone and the inactive carboxylated forms for both irinotecan and SN-38.[32]

SN-38 is inactivated by conjugation, which is primarily catalysed by the uridine diphosphate glucuronosyltransferase isoforms 1A7 (UGT1A7) and/or 1A9 (UGT1A9). The role of UGT1A1 has to be examined in more detail (figure 3).[33,34] This

isoenzyme is also responsible for the glucuronidation of substrates such as bilirubin and valproic acid.[35] Genetic enzyme deficiencies, such as Gilbert's syndrome or Crigler–Najjar syndrome type 1, result in impaired glucuronidation capacity. The molecular defects in Gilbert's syndrome are based on mutations within the five exons of the UGT1A gene locus.[35] The incidence of Gilbert's syndrome ranges from 0.5 to 15% in different ethnic groups, which explains why there is significant variability in UGT1A activity in human livers; this variability can result in a 17-fold interindividual difference between the minimum and maximum rates of SN-38 glucuronidation.[35] Patients with Gilbert's syndrome and other forms of genetic glucuronidation deficiency are at an increased risk of irinotecan-induced adverse effects, particularly gastrointestinal toxicity and leukopenia, if conventional doses are maintained.[36] Genotype screening is becoming increasingly feasible but is not yet routinely used. Thus, empirical irinotecan dose modification or the selection of another anticancer drug appears to be appropriate in patients with evidence of poor glucuronidation capacity (e.g. based on low levels of bilirubin glucuronide conjugates in the plasma).[37,38] In addition, drug interactions may occur if constitutive SN-38 glucuronidation capacity is modified (e.g. by drugs such as phenytoin). However, the relative extent of such an interaction has not been clearly elucidated.[39,40]

Irinotecan, SN-38 and its glucuronide metabolite, SN-38 glucuronide (SN-38G), are primarily excreted into the bile by the canalicular multispecific organic anion transporter (cMOAT, also known as multidrug resistance protein 2 [MRP2]), a member of the adenosine triphosphate group of transporters, but are also excreted by P-glycoprotein (also known as the multidrug resistance glycoprotein [MDR]).[42]

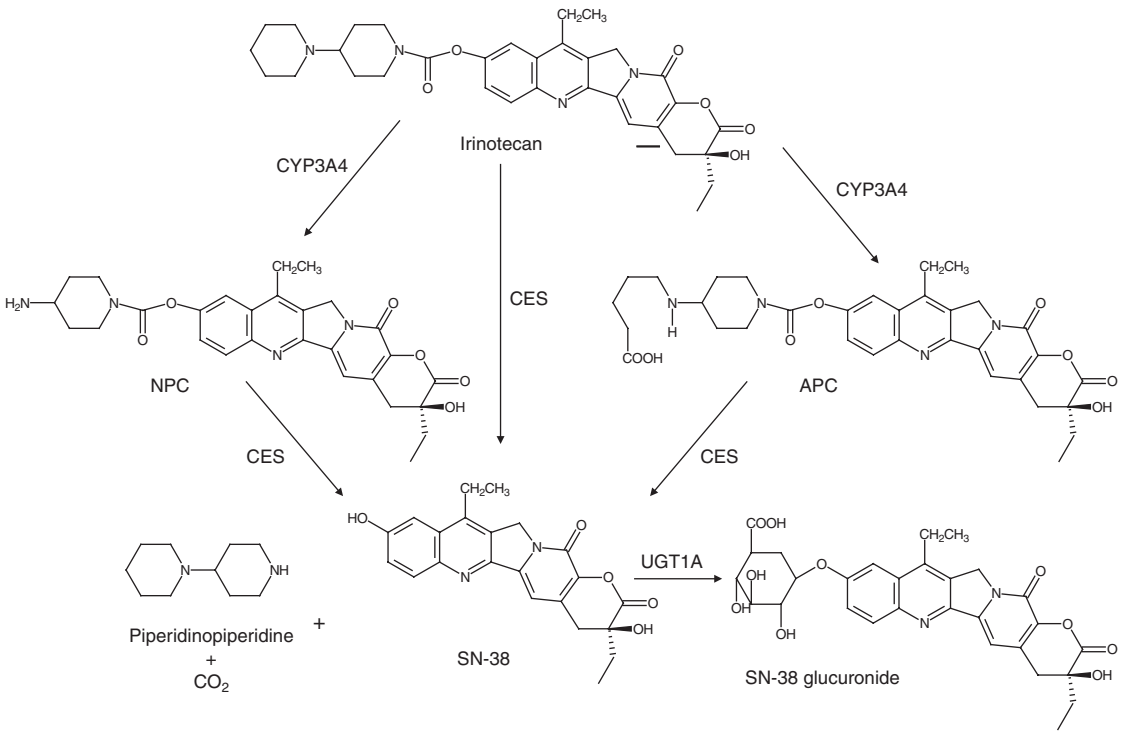


Fig. 3. Irinotecan is oxidised by the cytochrome P450 (CYP) 3A4 isoenzyme to produce 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) and 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin (NPC). NPC, APC and irinotecan are metabolised by carboxylesterases (CES) to produce the active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin). SN-38 is inactivated by uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A) to SN-38 glucuronide (reproduced from Sanghani et al.,[41] with permission).

Therefore, inhibitors of cMOAT and P-glycoprotein, such as ciclosporin, are able to reduce the clearance of irinotecan and SN-38. According to the study results published by Chester et al.,[43] coadministration of IV irinotecan and oral ciclosporin resulted in a >2-fold increase in the AUC of irinotecan, SN-38 and SN-38G. As a consequence, the ratio of SN-38 to irinotecan was not altered, suggesting a limited effect of this interaction on drug metabolism. During this coadministration, the maximum tolerated irinotecan dosage was 100 mg/m every 2 weeks. Interestingly, dose-limiting diarrhoea could not be observed in this trial, which may be related to the low SN-38 and SN-38G levels excreted into the gut lumen via the bile.[43]

SN-38G excreted into the bile can be deconjugated by bacterial glucuronidases in the gut to active SN-38.[44] SN-38 itself is able to undergo enterohepatic circulation that results in a second plasma peak of SN-38 after IV drug administration.[45] However, SN-38 released within the gut lumen has been suggested to be an important cause of delayed intestinal toxicity; in animal experiments, constitutive bacterial β-glucuronidase activity correlated with irinotecan-induced gut damage. In contrast, the prophylactic use of oral antibacterials (e.g. aminoglycosides, bacitracin or quinolones) resulted in attenuation of intestinal effects.[46]

Aminopentane-carboxylic acid (APC) is a further metabolite of irinotecan (figure 3); it is formed by oxidation of the terminal piperidine moiety, catalysed by CYP3A4. APC itself is not hydrolysed to SN-38 and is only a weak inhibitor of topoisomerase I.[47-49] However, potent CYP3A4 inducers (e.g. St John's wort, carbamazepine and phenytoin) or inhibitors (e.g. itraconazole, ketoconazole) may alter the pharmacokinetics of irinotecan significantly.[50] Other identified metabolites include 7-ethyl-10-(4-amino-1-piperidono)carbonyloxycamptothecin (NPC), 5-hydroxyirinotecan and RPR112526 (a decarboxylated product of the acid form of irinotecan lactone), which are altogether of minor quantitative importance.[47-49,51] However, based on the fact that different enzymes, namely CES2, UGT1A and CYP3A4, contribute significantly to irinotecan metabolism, large interindividual variability may be observed regarding the AUC of SN-38; this variability has been estimated to be as high as 70% among cancer patients treated with the same dose of irinotecan.[52]

After IV infusion of irinotecan over 30–90 minutes the estimated half-life of the parent compound and SN-38 ranges from 5 to 14 hours. In contrast, continuous 5-day IV drug infusion schedules, which are not yet being commonly used, result in prolonged half-lives (approximately 27 and 30 hours for irinotecan and SN-38, respectively).[47,48,53] Following IV administration, approximately 30% and 62% of the dose are excreted via the urine and faeces, respectively. Among excreted products, irinotecan accounts for 55% of the administered dose, followed by APC (10.5%), SN-38 (8.7%), SN-38G (3.3%) and NPC (1.5%).[52] Based on the importance of hepatic and biliary clearance, a negative correlation between serum bilirubin concentrations and the total body clearance of irinotecan has been observed. Following one case report in a patient with moderately impaired liver function,[54] it was calculated that, in order to achieve half-lives and maximum concentration values for irinotecan and SN-38 that were comparable to those observed in patients with normal liver function, the dose would have to be reduced to 100 mg/m^2 instead of the planned 350 mg/m^2 IV every 3 weeks. However, the corresponding AUCs were increased to a greater extent than expected, resulting in more severe leukopenia and delayed diarrhoea. The authors concluded that the dose should be further reduced to 30 mg/m^2 to improve tolerability in patients with moderate liver dysfunction.[54] In addition, phase I and pharmacokinetic study results revealed that patients with elevated direct bilirubin levels (up to 7 mg/dL) had an increased frequency of dose-limiting adverse effects, even though the starting dose was 145 mg/m^2 IV instead of 350 mg/m^2 IV.[55]

In conclusion, more detailed studies concerning irinotecan dose modification in patients with liver dysfunction are urgently needed. According to preliminary pharmacokinetic study results, standard IV doses of irinotecan every 3 weeks (350 mg/m^2) can be used in patients with bilirubin levels up to 1.5-fold the upper limit of normal (ULN), whereas 200 mg/m^2 IV should not be exceeded in patients with bilirubin levels 1.5–3.0-fold the ULN.[56,57]

The absolute bioavailability of irinotecan after oral administration is low and variable (10–20%).

Table III. Irinotecan-associated gastrointestinal discomfort

Characteristic	Acute (early) diarrhoea	Subacute (late) diarrhoea
Onset	On day of infusion	>24h after irinotecan infusion
Pathophysiology	Cholinergic syndrome	Hypersecretory in nature
Medical intervention	Prophylaxis: 0.25mg atropine Treatment: 0.25–1mg atropine	Prophylaxis (under debate): oral neomycin activated charcoa β-glucuronidase-inhibitors Treatment: loperamide (intensified) racecadodril octreotide opium tincture budesonide oral alkalinisation

Transintestinal transport of irinotecan and SN-38 by P-glycoprotein and CYP-mediated first-pass effects in the intestine account for this phenomenon.

1.3.2 Tolerability Profile

Myelosuppression and delayed diarrhoea represent the primary dose-limiting adverse effects of irinotecan.[5,29,30] The dose-limiting adverse effects of irinotecan depend largely on the dose schedule. Myelosuppression, particularly leukopenia and neutropenia, and more rarely thrombocytopenia and anaemia, has been observed following conventional IV doses. Gastrointestinal toxicity, particularly diarrhoea, is also common and can be distinguished as acute or subacute forms.

Leukopenia

Leukopenia is a dose-limiting adverse effect of irinotecan. Weekly IV doses (e.g. 100–125 mg/m^2) appear to produce a slightly greater incidence of grade 3–4 neutropenia compared with 3-weekly schedules (350 mg/m^2; 16–28% vs 14–22%).[4,32] The median leucocyte nadir occurs on day 15, with recovery 8 days later. Severe anaemia (haemoglobin concentrations <8 g/dL) and severe thrombocytopenia (platelet count $<50 \times 10^9$/L) occur in 15% and 2% of patients, respectively. In addition, some patients may develop eosinophilia during irinotecan treatment.[48,55]

Diarrhoea

Besides leukopenia, diarrhoea is the most important dose-limiting adverse effect related to irinotecan treatment. Acute diarrhoea occurs very early after drug administration and appears to be due to direct inhibition of the enzyme acetylcholinesterase.[58] The delayed-onset form of diarrhoea starts some days after drug administration, is hypersecretory in nature and its severity correlates with the concentrations of the active compound SN-38 in the plasma and bowel.[59]

The acute form of diarrhoea is short lasting and is part of the 'cholinergic syndrome' that is often accompanied by abdominal cramps, sweating, salivation, visual disturbances and lacrimation.[32] The recommended dose of atropine is 0.25mg IV for prevention or 0.25–1.0mg for acute treatment of patients with early cholinergic symptoms[32] (table III). As such symptoms have not been observed with other camptothecin derivatives, it can be speculated that these adverse effects are restricted to irinotecan, whose piperidino group bears some structural similarity to the potent nicotine receptor stimulant, dimethylphenylpiperazinium.[58] Coadministration of irinotecan and oxaliplatin on the same day has been shown to increase the occurrence of cholinergic syndrome.[60,61]

Delayed-onset diarrhoea of all grades of severity can be observed in nearly 90% of patients during the first three treatment cycles containing irinotecan.[32] The 'cholera-like syndrome' usually begins several days after completion of the infusion.[59] Grade 3–4 diarrhoea (grade 3: passing of 7–9 stools per day, incontinence or severe cramps; grade 4: passing of ≥10 stools per day, grossly bloody stools or a need for total parenteral nutrition) has been described in about 30–40% of patients, irrespective of whether they were treated on a weekly basis or every 3 weeks, with an average onset on day 6 (range: days

2–12).[59] Of the four major pathophysiological mechanisms of diarrhoea (osmotic, secretory, altered motility and exudative), irinotecan-induced watery diarrhoea appears to be primarily secretory, based on abnormal ion transport in the intestinal epithelial cells.[59,62]

There is increasing evidence that the extent and severity of irinotecan-induced gastrointestinal toxicity correlates with the concentration of the active compound SN-38 in the plasma and bowel.[8,44] The role of irinotecan pharmacokinetics in the plasma with regards to the prediction of the severity of irinotecan-induced diarrhoea has been highlighted by the introduction of a 'biliary index', which is defined as the calculated product of the AUC ratio of SN-38 to SN-38G and the total AUC. A preliminary study suggested using preventive measures very early in the course of treatment when the biliary index exceeded a defined value (e.g. 3.5 hxmg/L). However, this recommendation did not acquire broad acceptance because the biliary index cannot predict metabolic processes within the gut lumen.[8,63]

After biliary excretion, SN-38G undergoes deconjugation by bacteria-derived β-glucuronidase in the bowel. As a consequence, a strategy that has been proposed for reducing irinotecan-induced subacute diarrhoea is the inhibition of the intestinal microflora (e.g. with antibacterial agents or experimental selective β-glucuronidase inhibitors, such as saccharic acid 1.4-lactone).[64] According to results of a pilot project, neomycin prophylaxis was associated with less severe forms of subacute diarrhoea in six of seven treated patients compared with controls.[65] Besides bioactivation through bacterial β-glucuronidases, approximately 30% of the irinotecan dose is excreted via the bile in unchanged form, and thus, may be directly converted to SN-38 in the bowel by intestinal CES.[66] In conclusion, nonabsorbable inhibitors of β-glucuronidase, as well as of intestinal CES, could be of value to effectively circumvent irinotecan-induced delayed diarrhoea.[44]

Based on the fact that the equilibrium between the active lactone form and the ring-opened carboxylate form of irinotecan is pH dependent, oral alkalinisation with a mixture consisting of sodium bicarbonate (2.0 g/day), magnesium oxide (2.0–4.0 g/day), water (pH ≥7.2, 1.5–2 L/day) and ursodeoxycholic acid (300 mg/day), combined with 'controlled' defecation was used in a phase II trial to reduce subacute gastrointestinal toxicity.[67] The anticancer activity of irinotecan was maintained, whereas the incidence of delayed diarrhoea was significantly reduced compared with a non-randomised control group.[67,68]

The efficacies of several symptomatic antidiarrhoeal drug treatment regimens, including intensified loperamide, octreotide, racecadodril and budesonide, have been extensively assessed (table III). Loperamide is recommended when the first signs of subacute, late-onset diarrhoea occur;[59] loperamide not only delays small intestinal and whole gut transit, but also has some antisecretory activity in the human jejunum and colon.[59] The starting dose is 4mg, followed by 2mg every 2 hours, which is continued until the diarrhoea has stopped for at least 12 hours. However, general premedication with loperamide is not recommended. If loperamide alone is not effective enough, racecadodril 100mg three times daily can be added to treatment. Racecadodril belongs to a group of drugs that block cyclic adenosine monophosphate-mediated hypersecretion in the gut by inhibiting the intestinal enzyme, enkephalinase.[69] The somatostatin analogue octreotide is effective, particularly in loperamide-refractory patients.[70] Subcutaneous dosages of 100–150μg three times daily with dose escalation up to 500μg every 8 hours have been used successfully for at least 48–96 hours and have resulted in an improvement of diarrhoea by at least one WHO toxicity grade. Other second-line agents include tincture of opium.[71,72]

Oral budesonide has also been proposed to be beneficial in patients with subacute diarrhoea. Because of its 90% first-pass-mediated degradation in the liver, its systemic glucocorticoid activity is low.[73] Budesonide controls symptoms of diarrhoea in most patients with inflammatory bowel disease.[73] Preliminary data have suggested that the use of budesonide in patients with irinotecan-induced diarrhoea could reduce the severity of symptoms.[74] In addition, in a phase III trial budesonide 3mg three times daily significantly prevented irinotecan-induced diarrhoea.[75] As a consequence, budesonide appears to be an add-on option in patients who do not respond to high-dose oral loperamide.[75,76] Very

recently, activated charcoal has been suggested to be particularly beneficial for the prevention of irinotecan-induced diarrhoea. Activated charcoal may be able to absorb free lumenal SN-38, thereby reducing irinotecan-related intestinal toxicity. According to the results of a phase II trial, administration of activated charcoal resulted in a reduction in the occurrence of grade 3 to 4 diarrhoea, diminished the need for antidiarrhoeal medication consumption and allowed for increased irinotecan dose intensity.[77] However, whether activated charcoal is more advantageous than other methods of diarrhoea prevention needs further investigation.

Oral immunomodulators, such as interleukin-15 or Kampo medicine, may also be helpful to reduce irinotecan-related diarrhoea; however, randomised clinical trials are needed to assess their efficacy compared with placebo.[71]

1.3.3 Important Drug Interactions

St John's wort (300mg three times daily, starting 14 days before irinotecan administration) reduced the AUC of the active metabolite of irinotecan, SN-38, by 42% and diminished the severity of expected myelosuppression. Leukocyte and neutrophil counts were reduced by 8.6% and 4.3%, respectively, after coadministration of St John's wort with irinotecan, in contrast to reductions of 56% and 63%, respectively, following irinotecan monotherapy.[50,78] Considering potential interactions between irinotecan and various enzyme-inducing antiepileptic drugs, such as phenytoin, carbamazepine, oxcarbazepine and phenobarbital, all have been shown to increase the median clearance of irinotecan lactone and significantly decrease the median systemic exposure to SN-38 lactone.[50] The underlying mechanisms include CYP3A4 induction and UGT1A1 induction, as well as, in the case of phenobarbital, a possible increase in transporter activity leading to higher biliary drug excretion.[39] As a consequence, non-enzyme-inducing antiepileptics (e.g. gabapentin and dexamethasone) appear to be preferable as comedication if clinically indicated in patients who receive irinotecan, in order to circumvent complex drug interactions.[39,40,79]

In contrast, potent CYP3A4 inhibitors, such as ketoconazole and other triazoles, are able to reduce irinotecan clearance. However, the extent of dose modification needed in the case of coadministration of irinotecan and CYP3A4 inhibitors such as triazole antimycotic agents and some macrolides has not yet been determined (table II).[80]

1.4 Exatecan

Exatecan (DX-8951-f) is a novel synthetic water-soluble camptothecin derivative with a unique hexacyclic structure (figure 1). The recommended dosages of exatecan, according to phase II trials, are 0.5 mg/m/day and 0.3 mg/m^2/day as 30-minute infusions on 5 consecutive days for minimally pretreated and heavily pretreated patients, respectively (e.g. with anthracycline and taxane-refractory metastatic breast cancer, respectively).[81]

In contrast to irinotecan, exatecan does not require metabolic activation. According to *in vitro* experiments in various cancer cell lines, exatecan may be 6- and 28-fold more active as an anticancer drug than SN-38 and topotecan, respectively.[82] In addition, preclinical studies have revealed that the therapeutic index (maximum tolerated dose **:** minimum effective dose) of exatecan is approximately 2- to 10-fold greater than the corresponding values for irinotecan and topotecan.[83] In addition, exatecan may even be active in the presence of P-glycoprotein-mediated multidrug resistance.[4]

1.4.1 Clinical Pharmacokinetics

Pharmacokinetic studies indicate that, following a 30-minute IV exatecan infusion, the elimination half-life may be, on average, 8 hours. The amount of unchanged exatecan recovered in urine within 24 hours ranged from 1% to 16%, as the hepatic metabolism of this drug is extensive. This is in contrast to the structurally related topotecan.[81,84,85]

1.4.2 Tolerability Profile

Thus far, the dose-limiting adverse effects of exatecan have been identified as being neutropenia and liver dysfunction, whereas gastrointestinal discomfort is a rare event.[81,84,85]

1.5 Other Camptothecin Derivatives

Several other camptothecin analogues are currently under investigation, such as the water-soluble derivative lurtotecan (GI-147211) and the poorly water-soluble analogues IDEC-132 (9-amino-

camptothecin) and rubitecan (9-nitrocamptothecin), which can be given orally.[86-89] Further trials with topoisomerase I inhibitors include the feasibility of oral administration of topotecan and irinotecan, the use of a liposomal lurtotecan formulation (OSI 211 [NX211]) and the use of a pegylated derivative or other forms of the naturally occurring camptothecin, which are more soluble in aqueous solutions even at low pH values and may allow dose intensification.[90,91]

2. Podophyllotoxins

2.1 Mechanism of Action

Etoposide and teniposide (table IV) represent semisynthetic derivatives of podophyllotoxin, which was originally isolated from the root of the Indian Podophyllum plant. After extensive isolation procedures the most effective 'antileukaemic' factor was identified as being 4′-demethylepipodophyllin benzylidene glucoside (DEPBG). Etoposide, its water-soluble derivative etoposide phosphate, and teniposide, are semisynthetic analogues of DEPBG that have increased antineoplastic activity (figure 4). Etoposide is active in testicular carcinoma, non-Hodgkin's lymphoma and other lymphomas, ovarian carcinoma, SCLC and NSCLC, and neoplasms of unknown origin.[92] The pivotal indications for teniposide include malignant lymphoma and glioblastoma.[93,94]

Compared with the anthracyclines or rebeccamycin analogues, which also act as topoisomerase II inhibitors, etoposide and teniposide are neither able to intercalate sterically within DNA strands nor is their use associated with the chronic cardiotoxicity seen with anthracyclines.[96] Both drugs appear to act directly on the enzyme, which results in the stabilisation of a transient covalent complex formed between the enzyme and the DNA at break sites. During the presence of the epipodophyllotoxin derivatives, the enzyme-DNA intermediate cannot be reversed, resulting in DNA double strand breaks. Several studies have suggested that the activity of etoposide may be schedule dependent. The antiproliferative effect of etoposide on tumour cells appears to be greater when it is administered over several consecutive days rather than on a single day. At higher doses, podophyllotoxins may also act as spindle poisons.[97-99]

2.2 Etoposide

2.2.1 Clinical Pharmacokinetics

After IV administration of etoposide (e.g. 150 mg/m^2) the peak plasma concentration and half-life average 20 μg/mL and 7.1 hours, respectively. The drug clearance and volume of distribution have been determined to be 16 mL/min/m^2 and 7.1 L/m^2, respectively. Regarding plasma concentrations of etoposide, IV etoposide phosphate and IV etoposide have been shown to be bioequivalent, irrespective of whether conventional or intensified dose schedules have been used.[100,101] After IV administration, the prodrug etoposide phosphate undergoes rapid and complete hydrolysis catalysed by alkaline phosphatase. This conversion is not saturable even at high IV doses of up to 1200 mg/m^2 infused over 2 hours.[102,103]

If etoposide is taken orally, the absolute bioavailability is dependent on the dose. When the total etoposide doses are 50–100mg and 400mg, the average values have been determined to be about 75% and 50%, respectively.[104-107] If etoposide phosphate is taken orally, the average values appear to be somewhat higher.[108] However, the advantage of oral etoposide phosphate may be diminished when the prodrug is administered together with acid beverages, rather than with concomitant acid suppressive medication, based upon the importance of intestinal pH-dependent alkaline phosphatase activity during bioactivation.[109] Considering oral treatment with etoposide, marked interindividual variability has been observed in patients (e.g. children with relapsed acute lymphoblastic leukaemia).[110] As a consequence, therapeutic drug monitoring has been suggested to be beneficial in order to maintain effective cytotoxic drug concentrations over time and to simultaneously reduce the risk for systemic toxicity.[111] However, the translation of scientific data into everyday clinical practice remains a great challenge.

Approximately 96% of the dose of etoposide is bound to plasma proteins, whereas the unbound fraction averages 4%. There is a higher risk of myelotoxicity when the unbound fraction is in-

creased by factors such as hyperbilirubinaemia or hypoalbuminaemia, which may be of clinical relevance in patients with hepatic dysfunction or cachexia-inducing tumours.[112-118] In addition, the interindividual variability of drug concentrations has been suggested to be of importance in patients who receive high-dose IV etoposide followed by reinfusion of autologous peripheral blood stem cells.[119] If high drug concentrations persist over a longer period of time, the success of engraftment may be severely impaired. As a consequence, plasma drug concentration monitoring might be useful in order to identify patients at higher risk of graft failure.[119,120]

The renal clearance of etoposide is about 30–40% of the total plasma clearance. Hepatic etoposide metabolism is primarily mediated by CYP3A4, and less so by CYP3A5, and results in the formation of a catechol metabolite (3-hydroxyetoposide) via o-demethylation, which is able to undergo sequential one-electron oxidation reactions resulting in the corresponding semiquinone and quinone moieties (figure 5). In this context, it is still a matter of debate as to what extent catechol formation may contribute to the late adverse effects of etoposide, particularly its leukaemogenic activity.[121,122] Further metabolic pathways of minor quantitative importance include glucuronidation and hydroxyacid formation. Dose reductions of 33% and 50% have been recommended for patients with creatinine clearance values of 15–25 mL/min and <15 mL/min, respectively.[113,123] In patients with obstructive jaundice and a reduced glomerular filtration rate, a 50% empiric dose reduction may be required.[124]

So far, haemodialysis appears to be only moderately effective for the elimination of etoposide from systemic circulation.[125]

In patients with brain metastases, high IV doses of etoposide may be needed in order to achieve adequate drug concentrations in the CSF.[126] Intrathecal drug administration may be an alternative able to reduce the systemic toxicity associated with dose intensive chemotherapy; however, clinical experience is so far very scarce and is only based on case reports.[127]

A large interindividual variability in etoposide plasma concentrations has been observed following conventional doses.[128] As a consequence, some authors have suggested that by maintaining defined plasma concentrations of etoposide, treatment success might be optimised. For example, in patients with SCLC receiving etoposide 500 mg/m^2 IV as an infusion over 24 hours or as a 5-day schedule with 100 mg/m^2/day IV, the latter was associated with a higher response rate regarding partial remission as well as a favourable increase in median survival time, which might be correlated with longer exposure to concentrations exceeding 1 μg/mL.[128,129] However, more extended etoposide concentrations over time are also associated with a higher myelosuppressive burden, which limits, for example, either prolonged drug infusions or oral etoposide administration in routine practice.[111,113]

2.2.2 Tolerability Profile

A common adverse effect of etoposide and etoposide phosphate is dose-limiting myelosuppression. Leukopenia is the most common adverse effect

Table IV. Comparison of topoisomerase II inhibitors: etoposide and teniposide

Parameter	Etoposide (and etoposide phosphate)	Teniposide
Approved use	SCLC, NSCLC Lymphoma, AML Choriocarcinoma, advanced ovarian carcinoma Testicular cancers	CNS tumours, malignant lymphoma, bladder cancer
Conventional dosage recommendations	50–100 mg/m^2, d1–5 IV 100–200 mg/m^2/d PO, d1–5	30 mg/m^2, d1–5 40–50 mg/m^2, d1–3 100–130 mg/m^2, q1w
Pharmacokinetics	$t_{1/2\beta}$: 6–8h Metabolism via CYP3A4 Plasma protein binding: >94%	$t_{1/2\beta}$: 8h Metabolism via CYP3A4 Plasma protein binding: >99%

AML = acute myelogenous leukaemia; **CYP** = cytochrome P450; **IV** = intravenous; **NHL** = non-Hodgkin's lymphoma; **NSCLC** = non-small-cell lung cancer; **PO** = oral; **q1w** = every week; **SCLC** = small-cell lung cancer; $t_{1/2\beta}$ = terminal elimination half-life.

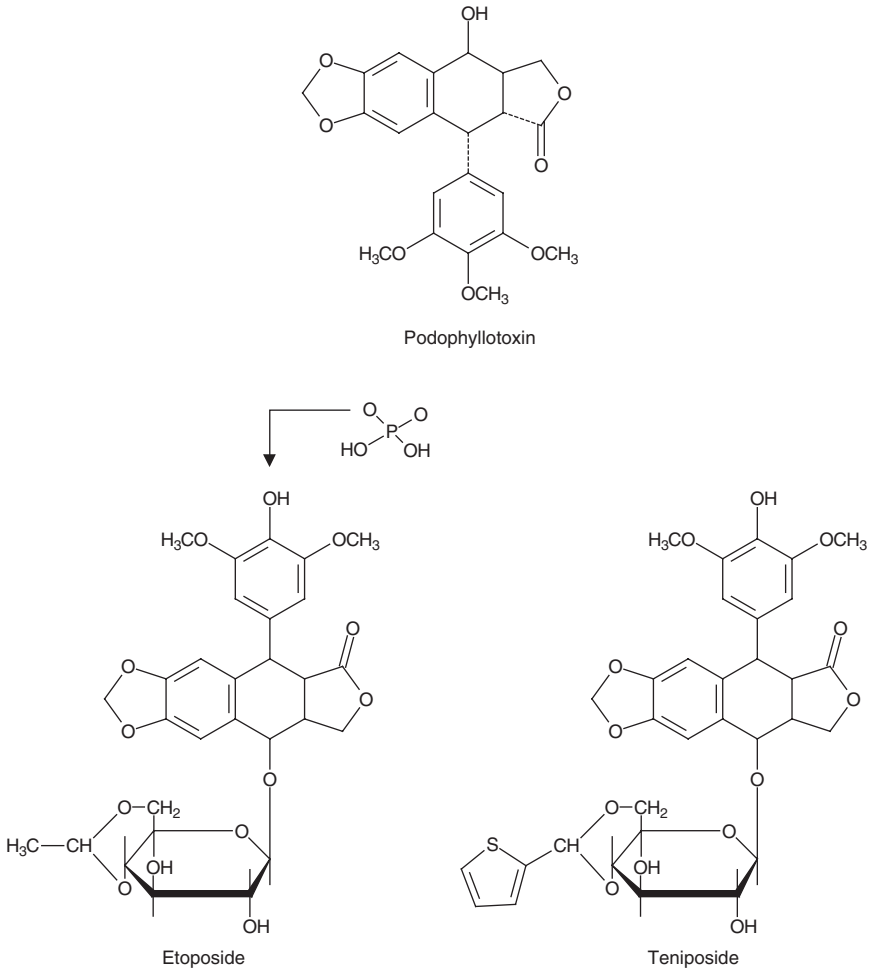


Fig. 4. The topoisomerase II inhibitor etoposide, its water-soluble derivative etoposide phosphate, and teniposide are semisynthetic derivatives of the natural compound podophyllotoxin.[95]

associated with oral and IV etoposide. Nadirs in neutrophil counts generally occur within 7–14 days after administration.[130] Thrombocytopenia occurs in 23% of etoposide-treated patients and about 9% develop platelet counts of $<50 \times 10^9$/L. Anorexia, vomiting and diarrhoea are generally of mild severity after administration of conventional doses of etoposide.[131] Mucositis is more severe in patients who receive IV doses of etoposide up to 1000 mg/m^2 than those who receive lower dosages.[120]

Hypersensitivity reactions are more common with etoposide and teniposide than with etoposide phosphate because the formulations of the former agents contain sensitising solubilisers.[132,133] The characteristic features of hypersensitivity reactions that occur after IV etoposide administration include bronchospasms, facial flushing, rashes, dyspnoea, fever, chills, tachycardia, chest tightness, cyanosis and changes in blood pressure (hypotension and hypertension).[134,135] However, very severe forms of hypersensitivity reaction, such as Stevens-Johnson syndrome, are extremely rare.[136] Anaphylactic-like reactions have occurred in 0.7–2% of patients after etoposide administration. With very few exceptions, patients recover quickly when the drug infusion is stopped immediately.[137] Hypersensitivity reactions

to etoposide or teniposide appear to be type I hypersensitivity (IgE mediated), with an onset of symptoms that usually occurs within minutes after IV administration. Several reports have suggested that premedication with an antihistamine and/or a corticosteroid may prevent further hypersensitivity reactions, even in patients with a history of previous complications.[138] However, this strategy should not be considered as routine practice when patients have previously had a severe hypersensitivity reaction, such as long-lasting bronchospasms or severe hypotension. Based on several case reports, etoposide could successfully be restarted in 78% of patients who had had experienced a hypersensitivity reaction, by slowly infusing the drug after premedication with an antihistamine and a corticosteroid.[139]

Hypersensitivity reactions to etoposide and teniposide are primarily related to the adjuvants used in the parenteral formulations, rather than to the drugs themselves. Etoposide formulations for parenteral use contain several adjuvants, including polysorbate 80, benzyl alcohol and polyethylene glycol, because the drug is rather insoluble in aqueous solutions. Polysorbate 80 has particularly been implicated as a causative agent for hypotension and metabolic acidosis, especially at higher doses.[132] In contrast, the structurally-related etoposide phosphate is highly soluble in aqueous solutions and, thus, no solubilising adjuvants are needed. Preliminary data suggest that the incidence of hypersensitivity reactions is lower with etoposide phosphate than with etoposide, which strengthens the hypothesis that adjuvants play a major role in the development of allergic reactions. According to case reports, patients who had a type I hypersensitivity reaction to etoposide could be successfully retreated with etoposide phosphate.[139,140]

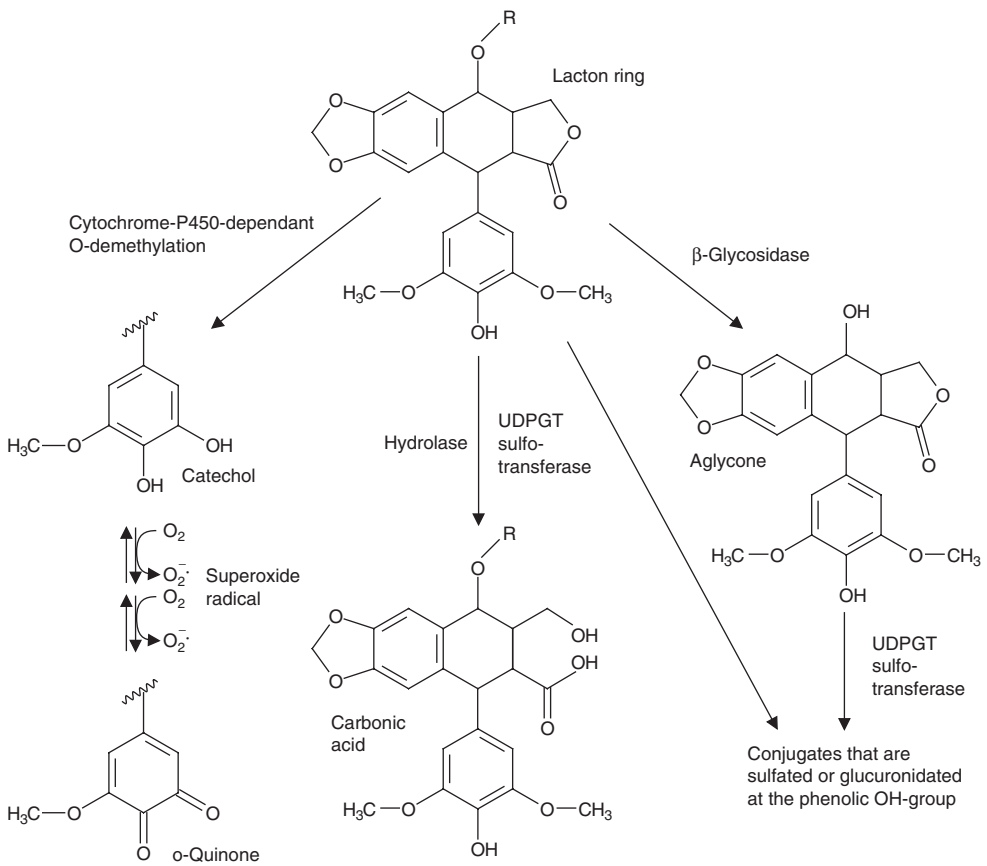


Fig. 5. Enzymatic biotransformation of the podophyllotoxin derivatives. **UDPGT** = uridine diphosphate-glucuronosyltransferase.[95]

However, cross reactivity to etoposide has been observed in patients with hypersensitivity reactions to teniposide, suggesting that the allergic reactions are not exclusively restricted to the use of the solvents. In addition, hypersensitivity reactions have also been reported after the use of oral etoposide.[141]

Neurotoxic symptoms are occasionally observed following treatment with etoposide (and teniposide), particularly at higher doses. Adverse nervous system effects, including headache, transient mental confusion and vertigo, may be related to the blood alcohol concentration, since teniposide and etoposide formulations both contain this solvent.[142] Peripheral neuropathy, mainly mild and infrequent, has been described after conventional doses of etoposide and teniposide. However, more severe forms of peripheral neuropathy have been reported during coadministration of etoposide and vinca alkaloids.[143,144]

Based on animal experiments, etoposide and teniposide can be classified as potential carcinogens.[145,146] In addition, both drugs appear to be important risk factors for the development of secondary acute myelogenous leukaemia, as they have considerable leukaemogenic activity.[147-156] Of 119 patients with advanced NSCLC, 24 survived for >1 year after treatment with etoposide and cisplatin, with or without vindesine. Of these 24 patients, four developed secondary acute myelogenous leukaemia at 13, 19, 28 and 35 months after the start of treatment. All four patients received a two-fold greater cumulative dose of etoposide (6.8 vs 3.0 g/m^2) than the rest of the study cohort.[132] Characteristically, podophyllotoxin-related secondary acute myelogenous leukaemia develops after a rather short latency (2–3 years) and differs from the malignancies caused by other drugs (e.g. alkylating agents) by its unique molecular marker, a balanced translocation involving the mixed-lineage leukaemia (MLL) gene on chromosome 11 ('11q23 abnormalities').[157] Southern blot analysis of enzyme-digested DNA from etoposide-treated cell lines and from peripheral blood cells after treatment with etoposide showed frequent rearrangements of MLL, but not of other genes. Altogether, the etoposide-related incidence of secondary acute myelogenous leukaemia in three retrospective case series has been described as ranging from 0.4% to 8.1%. Secondary leukaemias developed 9–68 months after the diagnosis of the first cancer.[158]

In conclusion, podophyllotoxin-containing regimens carry a small but significant risk of secondary acute myelogenous leukaemia, which, *per se*, is difficult to treat.[159] The risk may be increased by higher total cumulative doses (e.g. etoposide >2 g/m^2), weekly or twice weekly schedules, the concomitant administration of drugs that inhibit DNA repair, concomitant radiotherapy or the use of high doses of cisplatin. It has, therefore, been recommended that higher cumulative doses of etoposide should be used cautiously in low-risk diseases.[158]

2.3 Teniposide

2.3.1 Clinical Pharmacokinetics

After IV administration, teniposide is more extensively metabolised than etoposide. Plasma concentration monitoring has been proposed to be beneficial in patients receiving teniposide. For example, in one study the maintenance of steady-state teniposide concentration >12 μg/mL appeared to be important for higher clinical response rates in patients with recurrent leukaemia, lymphoma or neuroblastoma.[160] In those patients whose steady-state concentrations were maintained at >12 μg/mL, there was a shrinkage of the tumour, whereas patients with lower steady-state concentrations had a poorer response. Similar to etoposide, teniposide is a substrate of CYP3A4.[122] As a consequence, its clearance is increased by inducers of this enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampicin (rifampin) and St John's wort (table II). In contrast, competitive inhibitors of this enzyme may decrease the clearance of the podophyllotoxin derivatives (table II).[161,162]

The bioavailability of teniposide after oral administration is about 42% (range 20–71%). Although teniposide 50mg capsules have been suggested to be useful in clinical practice, no oral formulation has been approved thus far.[163]

2.3.2 Tolerability Profile

Leukopenia and thrombocytopenia occur in 65% and 80%, respectively, of patients after administration of conventional doses of teniposide.[94] Anorexia, vomiting and diarrhoea are generally of mild severity after administration of conventional doses

of teniposide.[164] Some data suggest that the overall incidence of hypersensitivity reactions to teniposide may be as high as 50%, if all forms of hypersensitivity reaction are taken into account. In the case of teniposide, the solubilising adjuvant polyoxyl-35 castor oil has been implicated as the pivotal causative agent.[132] However, in nine children who developed facial oedema and flushing after receiving teniposide, the drug itself degranulated basophils *in vitro* and caused histamine release, while polyoxyl-35 castor oil did not.[132] Teniposide is about 10-fold more potent than etoposide in causing DNA damage *in vitro* and *in vivo*. In 21 of 733 children with acute lymphoblastic leukaemia who were in remission and who received maintenance therapy with teniposide once or twice weekly in combination with other anticancer drugs, the risk of secondary acute myelogenous leukaemia was about 12-fold higher than in patients who had been treated with less intensive schedules (e.g. a short course of teniposide for induction chemotherapy).[155]

3. Dual Inhibitors of Topoisomerase I and Topoisomerase II

According to *in vitro* results, the administration of a topoisomerase I inhibitor in cancer cell lines resulted in a compensatory increase of topoisomerase II levels and *vice versa*.[165] As a consequence, schedule-dependent use of topoisomerase I and II inhibitors has been suggested to improve efficacy. However, based on overlapping myelosuppressive adverse effects, such a combined use of, for example, topotecan and etoposide, has not yet been established in clinical practice.[166-168] Based on preclinical study results, some drugs, such as F-11782, TAS-103, intoplicine and XR-5000, were considered encouraging dual topoisomerase I and II inhibitors; however, thus far none of these drugs have entered phase II or III trials.[169-171]

4. Conclusion

Camptothecin and podophyllotoxin derivatives are commonly used anticancer drugs in clinical oncology. Clinical pharmacokinetic studies have revealed substantial interindividual variabilities regarding AUC values and steady-state concentrations for all of the reviewed drugs (irinotecan, topotecan, etoposide and teniposide), which are – with the exception of topotecan – primarily because of the complex metabolic pathways involved in drug degradation. Some of the resultant metabolites contribute significantly to the observed toxicity of these drugs, which is of clinical concern. However, plasma concentrations of SN-38, the active metabolite of irinotecan, cannot predict gastrointestinal adverse effects accurately, because relevant levels of the active metabolite can also be formed in the gut by bacterial β-glucuronidases and intestinal CES. Regarding etoposide and teniposide, the extent of catechol formation over time during drug metabolism – although low – may be associated with a higher risk for secondary malignancies. In contrast, topotecan undergoes primarily renal excretion, with the parent drug being the most prominent substance recovered in the 24-hour urine. However, creatinine clearance varies considerably among patients, indicating that more precise renal function assessments than serum creatinine values are needed in order to accurately translate published recommendations for dose modification of topotecan into clinical practice. Medical oncologists have to be familiar with the clinical pharmacokinetics of topoisomerase I and II inhibitors and their possible drug interactions in order to modify the dose in time to avoid substantial subacute and late adverse effects.

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