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The Development of Camptothecin Analogs in Childhood Cancers

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Key Words. Topoisomerase I · Topotecan · Irinotecan · SN-38 · 9-aminocamptothecin · Camptothecin · Pediatrics

ABSTRACT
Camptothecin analogs, agents that target the intranuclear enzyme topoisomerase I, represent a promising new class of anticancer drugs for the treatment of childhood cancer. In preclinical studies, camptothecins, such as topotecan and irinotecan, are highly active against a variety of pediatric malignancies including neuroblastomas, rhabdomyosarcomas, gliomas, and medulloblastomas.

In this paper, we review the status of completed and ongoing clinical trials and pharmacokinetic studies of camptothecin analogs in children. These and future planned studies of this novel class of cytotoxic agents are critical to defining the ultimate role of topoisomerase I poisons in the treatment of childhood cancer.

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INTRODUCTION
There have been tremendous advances in the treatment of childhood cancer during the past several decades with resultant improvement in survival for the majority of children with cancer. However, this marked progress has not yet been realized for children with high-risk tumors, including those with malignant central nervous system (CNS) tumors, metastatic disease at diagnosis, or recurrent tumors. New treatment strategies, including the identification of chemotherapeutic agents with novel mechanisms of action, are prerequisites for the improvement of event-free and long-term survival of poor-prognosis pediatric tumors. The topoisomerase I poisons represent a promising new class of anticancer drugs for the treatment of childhood cancer. In this review we summarize the current status of the camptothecin analogs that have been evaluated to date in children.

Although the evaluation of camptothecin analogs in children is limited to the past decade, extracts containing camptothecin were first isolated more than 50 years ago from a native Chinese tree, Camptotheca acuminata. In the mid-1960s Wall and colleagues isolated camptothecin, the active component in the extracts, and elucidated its structure [1, 2]. Phase I clinical trials of sodium camptothecin followed in the late 1960s; however, further clinical development of sodium camptothecin was halted because in follow-up phase II trials there were severe and unpredictable toxicities and disappointing antitumor activity. The subsequent recognition of the novel mechanism of action of camptothecin in the late 1970s, followed by the development of water-soluble camptothecin analogs, led to a renewed interest in this class of compounds in the 1980s. Numerous phase I, II, and III clinical trials of topoisomerase I poisons have ensued. Two water-soluble camptothecin analogs recently have been approved by the Food and Drug Administration for clinical use: topotecan, as a second-line therapy for ovarian cancer or small-cell lung cancer, and irinotecan, for the treatment of colorectal carcinoma refractory to 5-fluorouracil or as initial therapy in combination with 5-fluorouracil for the treatment of metastatic colorectal cancer.

TOPOISOMERASE I FUNCTION
Topoisomerase I, an intranuclear enzyme that noncovalently binds to torsionally strained, supercoiled, double-stranded DNA, creates a transient single-strand break in the DNA molecule. This allows for the passage of an intact complementary DNA strand during replication, transcription, recombination, and other DNA functions [3]. The enzyme-bridged DNA breaks, also known as cleavable complexes, are then resealed by the topoisomerase I enzyme. Dissociation of the enzyme restores an intact, newly relaxed DNA double helix [4].

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Camptothecins are pentacyclic ring structures that require an intact α-hydroxyl lactone group in the E-ring for optimal interactions with the topoisomerase I enzyme [4]. The E-ring is labile in aqueous solutions, undergoing reversible pH-dependent hydrolysis to a relatively inactive open-ring carboxylate form that predominates at physiologic pH (Fig. 1). Substitutions at the C-7 and C-10 positions impact water solubility without interfering with biologic activity [5].

**Camptothecin Analogs: Structure Activity Relationships**

Camptothecins are pentacyclic ring structures that require an intact α-hydroxyl lactone group in the E-ring for optimal interactions with the topoisomerase I enzyme [4]. The E-ring is labile in aqueous solutions, undergoing reversible pH-dependent hydrolysis to a relatively inactive open-ring carboxylate form that predominates at physiologic pH (Fig. 1). Substitutions at the C-7 and C-10 positions impact water solubility without interfering with biologic activity [5].

**Camptothecin Analogs: Mechanism of Antitumor Activity**

The camptothecin analogs stabilize the cleavable complex between the topoisomerase I molecule and the free 3′-phosphate of the DNA. The resulting enzyme-linked DNA breaks cannot be religated as long as drug is present [6]. S-phase specific cytotoxicity results when the advancing replication fork and cleavable complex collide, leading to irreversible fork breakage and resultant DNA damage (Fig. 2) [7]. Unlike single-strand DNA breaks that are religated quickly upon removal of the topoisomerase I inhibitor, double-strand breaks persist for long periods of time following drug removal [8]. In the past, camptothecins have often been referred to as topoisomerase I inhibitors. However, they are not classic enzyme inhibitors since rather than directly altering the function of topoisomerase I, they convert this normal endogenous protein into a cellular toxin. Therefore, they are often preferentially referred to as topoisomerase I poisons [9].

**Camptothecin Analogs: Mechanisms of Resistance**

Resistance to camptothecin analogs in vitro is most commonly associated with either decreased levels of cellular topoisomerase [10, 11] or with gene mutations that downregulate or alter the topoisomerase I enzyme [12-15]. Reduced uptake of camptothecins due to overexpression of the multidrug resistance-associated protein [16-18] and to a lesser extent of P-glycoprotein [18, 19] has also been reported. However, the level of multidrug resistance to camptothecin analogs is markedly less than that observed with other multidrug resistance substrates [7]. Studies of in vivo mechanisms of resistance have not been performed.
**Preclinical Studies of Topoisomerase I Poisons**

Preclinical studies performed in vitro and in vivo reveal that the topoisomerase I poisons are active against a variety of adult and pediatric tumor cell types. Extensive studies in xenograft models demonstrate that topotecan and irinotecan are highly active against a variety of pediatric tumors including rhabdomyosarcoma, medulloblastoma, osteosarcoma, neuroblastoma, and glioma [20-23]. The antitumor activity observed in the xenografts is extremely schedule dependent: protracted, relatively low-dose schedules are more effective than more intense, shorter schedules in attaining partial or complete tumor regressions [20]. Direct translation of these findings into humans is complicated by the fact that there are marked species-specific differences in tolerance of topoisomerase I poisons. Mice tolerate much higher doses of these agents than humans due to an intrinsic pharmacodynamic resistance of murine marrow cells to topoisomerase I poisons [9, 24].

**Camptothecin Analogs: Clinical Development**

Clinical trials of topoisomerase I poisons in children were initiated in the early 1990s. Topotecan, the first camptothecin analog to undergo evaluation in children, is currently being investigated in phase III clinical trials. Irinotecan, which was not available for study in children until the mid-1990s, is currently being evaluated in phase II clinical studies. The results of the completed and ongoing clinical and pharmacokinetic trials of camptothecin analogs in children are summarized in the sections that follow.

**Topotecan**

**Phase I Single Agent Trials**

There have been multiple pediatric phase I studies of topotecan evaluating a variety of dosing schedules after either i.v. or oral dosing. Schedules of i.v. administration evaluated in solid tumor phase I trials include: A) 24-hour continuous i.v. infusion (CIVI) every 21 days [25]; B) 72-hour CIVI every 21 days [26]; C) 30-minute i.v. infusion, daily for 5 days, every 21 days [27], and D) 21-day CIVI, every 28 days [28]. In addition, three studies in which the i.v. formulation of topotecan was administered orally have been performed: A) daily dosing for 21 consecutive days, every 28 days [29]; B) daily dosing for 5 consecutive days per week for 3 weeks, every 28 days [29], and C) daily dosing for 5 consecutive days per week for 2 weeks, every 21 days [30]. A summary of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) for each of these trials is shown in Table 1.

In addition to the traditional phase I studies outlined above, investigators at St. Jude Children’s Research Hospital performed several phase I studies designed to achieve a target topotecan exposure, rather than an MTD [31, 32]. The target topotecan exposure for a phase I study in children with refractory solid tumors was based on the minimum effective lactone drug exposure, 150 ± 30 ng•hr/ml, defined in preclinical studies with xenograft models. Topotecan was given daily for 5 consecutive days for 2 weeks, every 28 days. Pharmacokinetic data obtained on day 1 were used to adjust the drug exposure on day 3. Additional pharmacokinetic samples were obtained on days 8, 10, and 12 and further dose adjustments were made, if necessary, to attain the desired target exposure [32]. Dose-limiting myelosuppression occurred at the initial target systemic exposure of 150 ± 30 ng•hr/ml (median dose 4 mg/m²/day) necessitating a reduction in the target exposure to 100 ng•hr/ml (median dose 3 mg/m²/day). Although patients in this study were not able to tolerate the desired target exposure, this strategy demonstrates the importance of the need for ongoing feedback between laboratory and clinical researchers in the drug development process.

*Furman et al.* used a similar approach in a phase I study of topotecan administered as a CIVI over 120 hours to children.

**Figure 2. Mechanism of action of the camptothecin analogs. Adapted with permission [5].**
with recurrent acute leukemia [31]. Dose escalations were
designed to achieve specified incremental increases in the
steady-state concentration of the lactone form of topotecan.
The investigators measured the steady-state topotecan concen-
tration, then modified the dose as necessary to obtain a con-
centration within 20% of the target exposure. The maximum
tolerated systemic exposure (MTSE) defined in this study was
a steady-state concentration of 4.0 ng/ml. The topotecan
dosage required to achieve this MTSE ranged from 1.6-2.1
mg/m²/day.

Toxicity
Myelosuppression, predominantly neutropenia, was the
DLT associated with topotecan in pediatric solid tumor
patients regardless of schedule or route of drug administra-
tion. Therefore, in some studies a maximum tolerated
topotecan dose following the addition of G-CSF was also
defined [26, 27]. In general, the addition of G-CSF allowed
only one additional dose level increase before thrombocy-
topenia became dose limiting. Mucositis was the DLT in
leukemia patients.

Nondose-limiting nonhematologic toxicities associated
with topotecan administration in children are similar to
those reported in adults. Nonhematologic toxicities
included: nausea and vomiting, alopecia, mucositis, ele-
vated liver transaminases, and skin rash/pruritus [25, 26, 31, 33]. As in adults, diarrhea was increasingly problematic
with protracted dosing schedules as well as after oral drug
administration [29, 34].

Phase I Studies of Topotecan in Combination with Other Agents
Phase I studies of topotecan in combination with other
anticancer agents or treatment modalities were initiated at an
early stage in the clinical development of topotecan. These
studies include two trials of cyclophosphamide administered
in combination with topotecan, a trial of carboplatin plus
topotecan, and a trial of topotecan administered in conjunction
with external beam radiation.

Based on the hypothesis that exposure to an alkylating
agent prior to a topoisomerase I poison would result in an
increased number of unrepaird DNA strand breaks and
enhanced cytotoxicity, the Pediatric Oncology Group initiated
a study of escalating doses of i.v. topotecan, daily × 5 days,
following administration of a fixed dose of i.v. cyclophos-
phamide (250 mg/m²/day), daily × 5 days [35]. The maximum topotecan
doze that could be administered in conjunction with cyclophos-
phamide and G-CSF was 0.75 mg/m². This dose is substantially
lower than the single-agent MTD of topotecan administered on
the same schedule, suggesting that there is synergistic toxicity
associated with this combination. Similarly, Kushner et al.
evaluated the combination of cyclophosphamide plus topote-
can; however, this group chose to investigate a more dose-
intensive regimen. Cyclophosphamide (4,200 mg/m²) was
given as a 48-hour CIVI with mesna plus topotecan (4.5 or 6
mg/m²) delivered as a 72-hour CIVI [36]. The DLT in both of
these studies was profound myelosuppression.

Heideman et al. performed a phase I study of carboplatin
and topotecan based on preclinical data suggesting that the
combination of a topoisomerase I poison and a platinating
agent would enhance cytotoxicity [37, 38]. Topotecan (0.3-
0.75 mg/m²/day) was administered as a 72-hour CIVI follow-
ing a 1-hour infusion of carboplatin administered at a fixed
systemic exposure (6.5 ng•hr/ml) [37]. Patients were strati-
fied by extent of prior myelosuppressive therapy. Patients
in the prior therapy stratum experienced dose-limiting
myelosuppression even at a very low topotecan dose of 0.3

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Schedule</th>
<th>MTD</th>
<th>DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blaney et al [25]</td>
<td>i.v., 24-h CI, q 21 days</td>
<td>5.5 mg/m²/day</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Pratt et al. [26]</td>
<td>i.v., 72-hr CI, q 21 days</td>
<td>1.0 mg/m²/day + G-CSF</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Tubergen et al. [27]</td>
<td>i.v., daily × 5, q 21 days</td>
<td>1.4 mg/m²/dose</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 mg/m²/dose + G-CSF</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Frangoul et al. [28]</td>
<td>i.v., 21-day CI, q 28 days</td>
<td>0.3 mg/m²/day</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Bowman et al. [29]</td>
<td>PO, qd × 21, q 28 days</td>
<td>0.8 mg/m²/dose</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myelosuppression, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Bowman et al. [29]</td>
<td>PO, (daily × 5) × 3, q 28 days</td>
<td>0.8 mg/m²/dose</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Dow et al. [30]</td>
<td>PO, (daily × 5) × 2, q 28 days</td>
<td>Not yet defined</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>1.6-2.1 mg/m²/day*</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Furman et al. [31]</td>
<td>i.v., 5-day CI, q 21 days</td>
<td>2.4 mg/m²/day</td>
<td>Typhilitis, mucositis, diarrhea</td>
</tr>
<tr>
<td>Furman et al. [32]</td>
<td>(daily × 9), q 21 days</td>
<td>2.4 mg/m²/day</td>
<td>Typhilitis, mucositis, diarrhea</td>
</tr>
</tbody>
</table>

*MTSE 4.0 ng/ml
mg/m²/day. In children with no prior history of myelosuppressive therapy, topotecan doses of 0.75 mg/m² plus carboplatin in conjunction with G-CSF are under study.

The results of a phase I trial evaluating topotecan given to children with intrinsic pontine glioma on a protracted dosing schedule in conjunction with external beam irradiation have recently been reported [39]. Topotecan was administered as a 30-minute infusion daily, Monday-Friday, for 33 days, followed 30-60 minutes later by involved field external beam irradiation (1.8 Gy/day single fraction, 59.4 Gy total). Topotecan doses ranged from 0.3-0.5 mg/m²/day with dose-limiting myelosuppression noted at the 0.5 mg/m² dose level. The recommended topotecan dose administered on this schedule in conjunction with radiotherapy for subsequent phase II trials is 0.4 mg/m²/day.

Phase II Topotecan Single-Agent Studies

Single-agent efficacy studies of topotecan in children with refractory solid or CNS tumors have been conducted. In many of these studies, a single intrapatient dose escalation or a limited interpatient dose escalation was performed because the MTDs identified in phase I studies in children were often lower than the MTDs defined in less heavily pretreated adults. Following the initiation of phase II pediatric studies, it quickly became apparent that the phase II pediatric population was experiencing minimal myelosuppression or other topotecan-related toxicity compared with the phase I population. Since children enrolled in the phase II trials were typically less heavily pretreated than those in the phase I study, this was not surprising. Results of the single-agent phase II studies of topotecan are briefly summarized below.

Two phase II studies of topotecan in children with refractory non-CNS solid tumors have been conducted. Blaney et al. evaluated the efficacy of topotecan administered as a 72-hour CIVI every 21 days [40]. An intrapatient dose escalation from 1.0 mg/m²/day to 1.3 mg/m²/day was performed in cycle 2 if there was no DLT in cycle 1. Minimal activity was seen in patients with neuroblastoma (1/24 complete response [CR]) and Ewing’s sarcoma/peripheral primitive neuroectodermal tumor (PNET) (1/26 partial response [PR]). No objective antitumor activity was seen in patients with osteosarcoma, rhabdomyosarcoma, or other soft tissue sarcomas. The other phase II topotecan study, conducted by the Pediatric Oncology Group, evaluated efficacy of the daily × 5, every-21-day schedule in 141 children with refractory solid tumors [41]. CRs occurred in 2/37 neuroblastoma patients and 1/3 PNET patients. PRs were observed in 1/29 Ewing’s sarcoma and 1/1 retinoblastoma patients. Although the overall objective response rate in this study was low, there were 29 patients, 13 of whom had neuroblastoma, with a mixed response (MR) or prolonged stable disease (SD). The median treatment duration for these patients exceeded 8 months. In addition, many of these patients had decreased requirements for narcotic analgesics or other signs of subjective improvement while receiving topotecan. As a consequence, it was concluded that topotecan demonstrated antitumor “activity” in patients with neuroblastoma.

Two phase II studies of topotecan in children with refractory or high-risk CNS tumors have also been performed [42, 43]. Topotecan was inactive in patients with glioblastoma multiforme, brain stem glioma, and medulloblastoma following administration as either a 24-hour CIVI every 3 weeks or a 72-hour CIVI every 3 weeks. However, in both studies there were some patients who experienced prolonged periods of SD. In the 24-hour CIVI study, one of two patients with low grade glioma had a PR and received 16 courses of therapy; and one patient each with malignant neuroepithelial tumor and optic glioma had SD for 41 and 22 weeks, respectively. Likewise, in the 72-hour CIVI study, there were two patients (astrocytoma, ependymoma) who completed the maximum 18 courses of topotecan.

Results of a Children’s Cancer Group phase II study of continuous 21-day-infusion topotecan in children with relapsed solid tumors are not yet known as this study is currently in progress.

Phase II Window Studies of Topotecan

Pappo et al. recently reported the single-agent activity of i.v. topotecan in patients with newly diagnosed metastatic rhabdomyosarcoma [44]. Topotecan, 2.0-2.4 mg/m²/day, daily × 5, every 21 days was administered for two courses prior to the initiation of standard therapy. Patients with at least a PR to topotecan in the phase II window subsequently received alternating courses of topotecan and standard therapy. The overall response rate to topotecan was 46% (CR 4%, PR 42%). Patients with alveolar rhabdomyosarcoma had a higher response rate than those with embryonal disease (65% versus 28%, p = 0.08). Although this study demonstrated that topotecan is effective against newly diagnosed patients with rhabdomyosarcoma, there was no apparent correlation between response to window therapy and survival.

Seibel et al. [45] evaluated the single-agent activity of i.v. topotecan administered daily × 5, every 21 days in newly diagnosed patients with metastatic osteosarcoma at dose levels of 3.0 mg/m²/day and 3.5 mg/m²/day. Patients tolerated these doses without experiencing DLT despite the fact that these doses were substantially higher than the phase I MTD on this schedule. There were only 2 PRs in the 26 patients who were treated in this window study.
Chintagumpala et al. performed a phase II window study of topotecan in newly diagnosed patients with high-grade gliomas who had residual measurable disease following initial surgery [46]. Drug was administered daily × 5 days with 21-day cycles. Patients received 3.5 mg/m²/day in cycle 1 and in the absence of DLT, 4.5 mg/m²/day in cycle 2. Patients receiving anticonvulsants were not eligible. No objective responses were observed in the 12 evaluable patients enrolled in this study.

Other Topotecan Studies
The Intergroup Rhabdomyosarcoma Study Group (IRSG) recently completed a phase II window trial of topotecan/cyclophosphamide in newly diagnosed patients with metastatic disease [47]. Topotecan 0.75 mg/m²/day and cyclophosphamide 250 mg/m²/day were administered daily × 5 days at week 0 and week 3. This window therapy was well-tolerated and yielded an overall response rate of greater than 50%. The response rate in this window study is similar to the response rate of topotecan alone. In the absence of a randomized study, the advantage of topotecan/cyclophosphamide versus topotecan or cyclophosphamide alone is not clear. Based on this study, the IRSG initiated a randomized study of vincristine/actinomycin/cyclophosphamide versus cycles of vincristine/actinomycin/cyclophosphamide alternating with vincristine/topotecan/cyclophosphamide (VAC versus VAC/VTC) in patients with intermediate-risk rhabdomyosarcoma.

Other ongoing phase II studies of topotecan include a study of topotecan administered as a 21-day CIVI, and a trial evaluating topotecan versus topotecan/cyclophosphamide in neuroblastoma patients unresponsive to a first regimen of conventional intensive chemotherapy. In addition, there is an ongoing Children’s Oncology Group/Pediatric Oncology Branch, National Cancer Institute phase II trial of intrathecal topotecan for patients with neoplastic meningitis or recurrent CNS leukemia.

IRINOTECAN (CPT-11)
Irinotecan is a pro-drug that is converted by carboxylesterase in the liver, intestinal tract, and some tumors to an active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin). SN-38 is 100- to 1,000-fold more potent than irinotecan [48].

Phase I Trials
Initial pediatric phase I trials of irinotecan evaluating a variety of dosing schedules have recently been completed. Schedules of administration evaluated in these studies include: A) a single dose, every 21 days [49]; B) daily dosing for 5 days, every 21 days [50]; C) daily dosing for 5 days per week for 2 weeks, every 21 days [51], and D) weekly dosing for 4 weeks, every 6 weeks [52]. In addition, a study following oral administration of the i.v. formulation administered daily for 5 days per week for 2 weeks, every 21 days has also been performed [53]. A summary of these trials is provided in Table 2.

Toxicity
Diarrhea and myelosuppression were the predominant DLTs after irinotecan administration [49-51, 53]. Other observed toxicities are similar to those reported in adults and include nausea and vomiting, transient elevation of serum transaminases, and diaphoresis with flushing during drug administration.

Phase I Studies of Irinotecan in Combination with Other Agents
Although agents with the same mechanism of action are not typically combined, results of a combination study of irinotecan plus topotecan were recently reported by investigators from St. Jude. This combination was evaluated because these agents have different spectrums of antitumor activity and potentially have different mechanisms of resistance. Unfortunately, protracted dosing of topotecan plus irinotecan resulted in a greater than expected amount of toxicity. As a

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**Table 2. Phase I studies of irinotecan in children with refractory solid tumors**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Schedule</th>
<th>MTD (mg/m²/dose)</th>
<th>DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vassal et al. [49]</td>
<td>90-min i.v infusion q 21 days</td>
<td>600</td>
<td>Cardiac failure*, infection</td>
</tr>
<tr>
<td>Furman et al. [51]</td>
<td>i.v., (daily × 5) × 2, q 21 days</td>
<td>20</td>
<td>Diarrhea and/or abdominal cramps</td>
</tr>
<tr>
<td>Blaney et al. [50]</td>
<td>i.v., daily × 5, q 21 days</td>
<td>39 (heavily treated)</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 (less-heavily treated)</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Kerr et al. [52]</td>
<td>i.v., weekly × 4, q 6 weeks</td>
<td>125 (heavily treated)</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125+ (less-heavily treated)</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>Radomski et al. [53]</td>
<td>PO, (daily × 5) × 2, q 21 days</td>
<td>40</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

*prior anthracyclines and mediastinal irradiation
result, safe doses of these two agents in combination could not be defined [54].

The Children’s Oncology Group is currently performing several phase I studies of irinotecan in combination with other cytotoxic agents including: irinotecan administered weekly for 4 weeks every 6 weeks in combination with a fixed dose of cisplatin on day 1; and, a phase study of a fixed dose of irinotecan given daily for 5 days, every 21 days plus vincristine given weekly for 5 weeks.

Phase II Irinotecan
A Children’s Oncology Group phase II study of a 50 mg/m²/dose of irinotecan, given daily for 5 days every 21 days in children with refractory solid or CNS tumors is ongoing. Pharmacokinetic studies have been incorporated into this trial to evaluate whether or not there are pharmacodynamic correlates with either toxicity or response in children. In addition, pharmacogenetic studies to evaluate UGT1A1 genotype are an important component of this phase II trial (see Pharmacokinetics/Pharmacodynamics section below).

9-AMINOCAMPTOTHECIN (9-AC)
The Pediatric Oncology Group performed a phase I trial of 9-AC administered as a 72-hour CIVI in children with refractory solid tumors [55]. Dose levels ranged from 36-62 µg/m²/hour with an MTD of 52 µg/m²/hour. The DLT was myelosuppression. Nausea and vomiting were the most common nonhematologic toxicities. A PR was observed in a patient with adenocarcinoma of the colon, and an MR of 11 months duration occurred in a patient with myxoid angioblastoma. Similar to the other topoisomerase I poisons, there was marked interpatient variability in pharmacokinetic parameters. Recent xenograft data have shown that 9-AC exposure measured at doses resulting in antitumor activity exceeds that reported at MTDs in phase I studies, perhaps explaining the disappointing antitumor activity [56]. Phase II studies of 9-AC have not been pursued due to the relative greater potency of other camptothecin analogs in pediatric tumors.

### Pharmacokinetics/Pharmacodynamics
Not only are there differences in the toxicity profiles of the camptothecin analogs, but there is also substantial variation in their pharmacokinetic and pharmacodynamic profiles (Table 3). For example, the amount of drug present in the active lactone form varies among analogs, with levels lowest with 9-AC (~11%) [55] and topotecan (10%), and highest for SN-38, the active metabolite of irinotecan (~50%). Likewise, there are differences in the cerebrospinal fluid penetration between camptothecins that are probably related to relative differences in protein binding; topotecan has the highest CSF penetration (~30%) [57] and 9-AC the lowest (<4%) [58]. In adults, the spectrum of clinical activity differs among the various camptothecins; this may be related to the noted differences or other potential differences at the molecular level. It remains to be seen whether or not the spectrum of clinical activity for camptothecins in children will be similar or different among the various analogs. Some specific details about the pharmacokinetics of topotecan and irinotecan are outlined below.

### Topotecan
Data from the phase I studies showed that topotecan pharmacokinetics in children are linear with dose; however, there is marked interpatient variability in drug clearance [24, 59]. Pharmacokinetic studies following oral administration of the i.v. formulation of topotecan reveal that, although there is considerable interpatient variability in drug disposition and bioavailability, there is relatively little intrapatient variation [60]. The mean terminal half-life of topotecan is between 3 and 5 hours. The primary route of elimination is renal [24, 31, 61], although a small fraction of topotecan is eliminated following oxidative metabolism to an N-desmethyl metabolite [62]. This becomes clinically important in patients receiving concomitant medications that induce oxidative metabolism, e.g., anticonvulsants such as phenytoin, because there is a subsequent marked increase in clearance and an overall decrease in lactone exposure that may affect drug efficacy [63]. Thus, higher doses of topotecan may be

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**Table 3. Pharmacokinetic parameters for camptothecin analogs in children**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Terminal half-life (h)</th>
<th>Clearance (L/h/m²)</th>
<th>AUC*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Drug</td>
<td>Lactone</td>
<td>Total drug</td>
</tr>
<tr>
<td>Topotecan</td>
<td>2.3 ± 0.5</td>
<td>2.9 ± 1.1</td>
<td>9.8 ± 3.9</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>3.6-5.7</td>
<td>2.6</td>
<td>19.7-27.7</td>
</tr>
<tr>
<td>SN-38</td>
<td>10.3</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>9-AC</td>
<td>8.1 ± 3.8</td>
<td>7.1 ± 3.9</td>
<td>~25</td>
</tr>
</tbody>
</table>

*AUC = area under concentration versus time curve*
required for patients receiving such medications. Impaired renal function decreases topotecan clearance, necessitating a dosage reduction [64]; however, mild to moderate hepatic dysfunction does not appear to affect drug disposition [65].

**IRINOTECAN**

There is substantial interpatient variation in the disposition and terminal half-life of irinotecan (half-life 5-14 hours) and its active metabolite, SN-38 (half-life 6-30 hours). Kinetics appear to be linear over the standard dose range administered to adult patients (125-350 mg/m²/dose). However, studies in children and adults over a wider dose range (20-750 mg/m²/dose) suggest that kinetics may be nonlinear at higher doses due to saturation of irinotecan metabolic pathways and biliary transport mechanisms [51, 66, 67]. With i.v. administration, conversion of irinotecan to SN-38 is inefficient (<10% of the dose) [68, 69]. Oral irinotecan is rapidly absorbed and more efficiently converted to SN-38 due to first-pass metabolism, but plasma drug and metabolite concentrations are highly variable [70].

Carboxylesterase enzymes in the liver and intestinal tract convert irinotecan to SN-38 [71-73], which is subsequently metabolized by hepatic uridine diphosphate glucuronosyltransferases (UGT), to form SN-38 glucuronide (SN-38G) [74]. UGT isoenzyme 1A1 (UGT1A1), the primary enzyme involved in the glucuronidation of SN-38 [75], is the same isoenzyme that glucuronidates bilirubin [76]. Thus, patients with an elevated bilirubin level, a partial UGT1A1 deficient state (e.g., Gilbert’s or Crigler Nijjar syndromes), or patients who are receiving medications that inhibit UGTA1A (e.g., valproic acid) may be at risk for increased drug-related toxicity, since high intraluminal concentrations of SN-38 are believed to be the primary cause of treatment-related diarrhea [77].

Irinotecan is also converted by cytochrome P450 isozyme CYP3A4 to form two minor metabolites (APC and NPC) [78, 79]. Agents that induce CYP3A4, (e.g., phenytoin, phenobarbital, and carbamazepine) have been shown to lower systemic exposure to irinotecan and SN-38 through increased irinotecan clearance and decreased production of SN-38. Ongoing clinical trials and anecdotal reports in brain tumor patients who are receiving anticonvulsants demonstrate that such patients may tolerate very high doses of irinotecan [80-83].

**OTHER CAMPTOTHECIN ANALOGS**

There are a number of other camptothecin analogs that are in earlier stages of preclinical or clinical development including DX-8951f, a synthetic water-soluble camptothecin, and karenitecin (BNP1350), a highly lipophilic topoisomerase I poison. Both of these agents have demonstrated increased potency in vitro against a variety of adult and pediatric cell lines compared with either SN-38 or topotecan [84-86]. Preliminary results of a pediatric phase I study of DX-8951f recently have been reported [87] and a phase I study of karenitecin is in progress.

**CONCLUSION**

Topoisomerase I poisons are an exciting new class of anticancer drugs with promising evidence of antitumor activity for children. The spectrum of clinical activity for children with recurrent or refractory disease, as well as the ultimate role and contribution of topoisomerase I poisons in the front-line treatment of children with cancer, have not yet been defined. However, there are ongoing studies or planned future trials that will provide answers to these important issues. Major challenges facing pediatric oncologists in the development of topoisomerase poisons include: the selection of the most desirable camptothecin analog; selection of the best drug combination(s) for clinical study; and selection of the optimal dosing schedule for maximum efficacy and minimum toxicity. There are obvious inherent limitations to the design and conduct of clinical trials of topoisomerase poisons in children due to the limited population available for clinical trials. Therefore, ongoing evaluation and re-evaluation of preclinical, clinical, and laboratory data pertaining to both current and new topoisomerase I poisons are critical to the most effective and efficient development of this promising new class of agents for the pediatric population.

**REFERENCES**

6. Hertzberg R, Carafa M, Holden K et al. Modification of the hydroxy lactone ring of camptothecin: inhibition of mammalian...


