

# Topotecan and Irinotecan in the Treatment of Pediatric Solid Tumors

Yoshiaki Tsuchida\*<sup>1</sup> and Toshiji Shitara<sup>2</sup>

From the Departments of <sup>1</sup>Surgery and <sup>2</sup>Hematology/Oncology, Gunma Children's Medical Center, Gunma, Japan.

**Abstract:** There have been significant advances in the treatment of neuroblastoma and rhabdomyosarcoma, but the clinical results are still poor, especially after tumor relapse. In addition to this, rhabdomyosarcoma does worse if localized tumors occur in unfavorable sites. Therefore, new chemotherapeutic agents have been sought, and the effects of 9-dimethylaminomethyl-10-hydroxycamptothecin (topotecan) and 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonylcamptothecin hydrochloride (irinotecan) were studied preclinically and clinically during the past decade not only in adults but also in children. Irinotecan and topotecan inhibit DNA topoisomerase I, which is an essential nuclear enzyme that relaxes torsionally strained duplex DNA, enabling replication and transcription. These agents were reported to be effective against various human malignancies in adults. Among these camptothecin derivatives, topotecan and irinotecan are the most widely used clinically, and at present irinotecan appears to be more promising in the treatment of childhood solid tumors such as rhabdomyosarcoma and neuroblastoma. The recommended dose and administration schedule differ among clinical trials. For example, 1-day, 3-day, and 10-day regimens have been used. In the present article, the clinical effectiveness of topotecan and irinotecan with different administration schedules are reviewed in the US, French and Japanese literature, and the authors propose which agent and which administration schedule of these agents are the most effective in the treatment of pediatric solid tumors.

**Keywords:** Topotecan, irinotecan, neuroblastoma, rhabdomyosarcoma, leiomyosarcoma, phase-II trials.

## DEVELOPMENT OF TOPOTECAN AND IRINOTECAN

Significant advances in survival rates have been achieved in the treatment of several pediatric solid tumors such as advanced neuroblastoma [1,2] and rhabdomyosarcoma [3,4], but the clinical results are still unsatisfactory, especially in patients with disseminated disease. Therefore, numerous new agents such as paclitaxel, ftemustine, busulfan, mitomycin C, ifosfamide, and bleomycin have been investigated for their efficacy in preclinical studies [5-7], and only a few were found to be sufficiently promising to be incorporated in clinical trials. The topoisomerase I inhibitors topotecan and irinotecan are examples of such promising agents.

In the Yangtze River basin of China, elderly Chinese are aware that leaves of the tree *Camptotheca acuminata* are effective against human gastric cancer. The antitumor activity of 20(S)-camptothecin, a plant alkaloid isolated from *C. acuminata*, was first studied more than 20 years ago [8]. Although 20(S)-camptothecin is insoluble in aqueous vehicles, extensive investigation has identified more soluble and active camptothecin analogs. The water-soluble analog, 9-dimethylaminomethyl-10-hydroxy-camptothecin (topotecan) demonstrate sbroad-spectrum activity against rodent tumor models [9] and significant therapeutic activity against some human colon adenocarcinoma xenografts [10].

Another water-soluble derivative of camptothecin, 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyl-camp

tothecin hydrochloride trihydrate (irinotecan, CPT-11), was synthesized [11]. Irinotecan and topotecan [12] inhibit DNA topoisomerase I, which is an essential nuclear enzyme that relaxes torsionally strained duplex DNA, enabling replication and transcription. However, irinotecan is a masked compound and, as opposed to topotecan, the hydrolysis of the piperidino-piperidine side-chain by carboxylesterase leads to the formation of the active metabolite SN-38 [13]. *In vitro* studies have demonstrated that SN-38 is the most potent active drug among the topoisomerase I inhibitors so far available for clinical development [14].

## PRECLINICAL STUDIES OF TOPOTECAN

Studies in mice bearing human solid tumors have shown that topotecan is among the most active anticancer drugs. Significant objective responses have been obtained in colon carcinoma [10,15], rhabdomyosarcoma [10,15,16], neuroblastoma [17], osteosarcoma [10], and brain tumors [15,16]. In addition, studies in these xenograft models have shown that antitumor activity is highly dependent on the administration schedule, including dosage. Responses were frequently observed when the agent was given daily at low doses for protracted periods [15,17]. In some studies, prolonged administration induced responses in xenografted tumors that had been unresponsive to intermittent administration of the agents at high doses [15].

## CLINICAL STUDIES OF TOPOTECAN

### Phase I Studies

Phase I studies of topotecan have investigated various administration schedules and doses. Based on the S-phase specificity of topotecan, most phase I trials explored

\*Address correspondence to this author at the Department of Surgery, Gunma Children's Medical Center, 779 Shimohakoda, Hakkitsu, Seta-gun, Gunma 377-8577, Japan; Fax: +81-279-52-2045, Tel.: +81-279-52-3551, E-mail: tuchida@gcmc.pref.gunma.jp

schedules that result in prolonged exposure to maximize the drug's interaction with topoisomerase I during the S-phase. The regimens investigated included, for example, one 24-h infusion every 3 weeks, continuous 72- to 120-h infusion every week or every other week, and 30-min infusion for 5 days every 3 weeks [18,19]. The results of those studies suggested that prolonged exposure induces more responses than short-term exposure at higher concentrations. The regimen recommended for most phase II studies is 1.5 mg/m<sup>2</sup> daily for 5 days every 3 weeks [20]. With these schedules and doses, the dose-limiting toxicity was found to be myelosuppression [20].

In children, phase I studies have also explored different schedules of prolonged administration (for example, 72-h infusion [12], 120-h infusion [21], or daily  $\times$  5 [22]). The dose-limiting toxicity in most pediatric trials was also myelosuppression, and the maximum tolerated dose (MTD) is 1.4 mg/m<sup>2</sup> per day for 5 days, if granulocyte-colony-stimulating factor is not given [22]. A 10-day topotecan administration schedule ( $[\text{qd} \times 5] \times 2$ ) was also successful [23,24].

### Phase II Studies

Most adult phase II studies of topotecan given as a single agent administered 1.5 mg/m<sup>2</sup> daily for 5 days every 3 weeks (the most effective schedule in phase I) to patients with advanced or recurrent disease [20]. In adults, many patients with lung cancer or other advanced disease are enrolled in phase II from the beginning even though they are previously untreated [20]. In randomized trials, this schedule has yielded better responses than schedules of intermittent administration [25]. The best responses have been obtained in patients with advanced ovarian carcinoma [25-31] and in patients with advanced lung cancer [32-36]. Minimal responses have been observed in patients with colorectal cancer and gastric cancer [20]. Finally, as many as 43% of previously untreated patients with myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) showed complete responses to topotecan given by continuous infusion for 5 days [37]. These responses were associated with the disappearance of genetic abnormalities characteristic of MDS/CMML [37].

There have been two phase II studies of topotecan in children. Blaney and co-workers administered topotecan as a 72-h continuous infusion at a dosage of 1 mg/m<sup>2</sup>/day to children with refractory neuroblastoma or sarcomas [38]. The antitumor activity was minimal on this schedule, as responses were obtained in only 1 of 26 patients with neuroblastoma and in only 1 of 25 patients with primitive neuroectodermal tumor (PNET) [38]. A protracted schedule was used in a Pediatric Oncology Group Study in which children with refractory solid tumors were given 2 mg/m<sup>2</sup>/day for 5 days. The dose administered was also greater in the latter schedule, and complete (CR) and partial responses (PR) were observed in patients with neuroblastoma, PNET, and retinoblastoma [38,39]. Two up-front window studies used the same dosage and schedule. A Pediatric Oncology Group study obtained objective responses in 38% of children with stage IV neuroblastoma [40]. An Intergroup Rhabdomyosarcoma Study Group phase

II study in previously untreated patients with rhabdomyosarcoma obtained an overall response rate of 45% (67% for alveolar rhabdomyosarcoma) [41]. These results confirmed that topotecan given on a protracted schedule has a definite role in the treatment of childhood solid tumors such as neuroblastoma, PNET, and rhabdomyosarcoma.

### PRECLINICAL STUDIES OF IRINOTECAN

Irinotecan, a water-soluble prodrug, has been shown to have broad-spectrum activity against experimental adult and pediatric tumor models [15,42-48]. Significant objective responses to irinotecan have been observed in pediatric rhabdomyosarcoma [10,15,16,48], neuroblastoma [13,17,49-51], brain tumors [15,16,52], and osteosarcoma [10]. In particular, rhabdomyosarcoma and neuroblastoma showed irinotecan sensitivity, and in the history of pediatric oncology, this is the first time that the clinical development of a new anticancer drug started with specific preclinical data obtained from pediatric tumor models. Irinotecan is clearly very active against pediatric tumor xenografts. Can these preclinical results predict the efficacy of irinotecan in children with solid tumors? Irinotecan is biotransformed *in vivo* to its active metabolite SN-38 by carboxylesterase. Murine plasma contains carboxylesterase, while human plasma does not [13]. Therefore, phase I and II clinical trials were particularly needed.

### CLINICAL STUDIES OF IRINOTECAN

#### Phase I Studies

Most of the phase I studies of irinotecan in adults investigated 90-min infusions administered every week for 3 to 4 weeks or once every 3 weeks [53,54].

Four phase I trials of irinotecan in children were conducted in the USA, France, and Japan [55-58]. Furman and co-workers [55] recommended administration of irinotecan 20 mg/m<sup>2</sup>/day for 5 consecutive days, repeated once after 2 days off (10-day administration in total) based upon their results of irinotecan experiments in an *in vivo* system. Similarly, Blaney *et al.* studied the administration of irinotecan for 5 consecutive days, repeated every 3 weeks [56]. On the other hand, Vassal and co-workers [57] reported that the MTD of irinotecan in children was 600 mg/m<sup>2</sup> when given as a 120-min intravenous infusion every 21 days. Mugishima *et al.* [58] determined that the MTD of irinotecan for children was between 160 mg/m<sup>2</sup>/day and 180 mg/m<sup>2</sup>/day administered over 3 consecutive days, repeated once after 25 days off. The MTDs obtained in those studies are currently recommended for phase II trials by the respective study groups (Table 1).

#### Phase II Studies

A variety of phase II trials of irinotecan have been conducted and this agent has been reported to be effective against various adult human malignancies, including lymphoma, gastric cancer, small cell lung cancer, non-small cell lung cancer, cervical cancer, epithelial ovarian cancer, and colorectal cancer [59-65].

The doses and administration schedules, currently recommended for phase II trials of irinotecan in children

**Table 1. Recommended Administration Schedules for Phase II Trials of Irinotecan in Children and Their Tentative Clinical Results.**

Phase I Trials		Phase II Trials
Authors	Recommended Administration Schedules for Phase II	Remarks
Mugishima <i>et al.</i> [58] (Japan)	180 mg/m <sup>2</sup> /day for 3 consecutive days; repeated every 4 weeks	On-going
Furman <i>et al.</i> [55] (USA)	20 mg/m <sup>2</sup> /day for 5 consecutive days repeated once after 2 days off; repeated every 4 weeks	21% response rate; 2 CR/2 PR in 19 patients (Cosetti <i>et al.</i> [66])
Blaney <i>et al.</i> [56] (USA)	40 mg/m <sup>2</sup> /day for 5 consecutive days; repeated every 4 weeks	On-going
Vassal <i>et al.</i> [57] (France)	600 mg/m <sup>2</sup> /day for one day; repeated every 3 weeks	Disappointing in neuroblastoma (Vassal <i>et al.</i> [67])

(Table 1), have merits and demerits [55-58,66]. Cosetti *et al.* [66] saw 4 objective responses (2 CR and 2PR) (21.1% response rate) in 19 valuable patients treated on the administration schedules developed by Furman *et al.* [55]. Protracted use (intravenous or oral) of irinotecan might be recommended because of its consistent effectiveness, but the use of irinotecan over 12 days could be somewhat burdensome for patients and clinicians. On the other hand, the single-day administration of irinotecan yielded disappointing clinical results in phase II trials in relapsed neuroblastomas [57], and therefore Vassal *et al.* concluded that their dosing schedule of irinotecan [57] showed no clinically useful activity. Vassal *et al.* further mentioned that because the majority of children had received very intensive induction treatment and retinoids, it was unlikely that a single agent in a phase II setting would demonstrate activity [67]. They considered that they needed to evaluate neuroblastoma in a different setting in the future to prevent clinically important agents from being missed [67].

Cosetti *et al.* [66] observed CR or PR in 3 of 4 patients with relapsed rhabdomyosarcoma on the irinotecan administration schedule of Furman *et al.* [55], and this observation coincides with Shitara *et al.*'s results in a rhabdomyosarcoma trial even though they used a different administration schedule [68]. Shitara and collaborators reported that administration over 3 consecutive days may have an advantage over other schedules. They administered irinotecan 180 mg/m<sup>2</sup>/day for 3 consecutive days having already confirmed protracted plasma concentrations of irinotecan with their 3-day administration schedule [68]. With this administration schedule, which differs from those in the USA and France, PR was observed in 38.5% of the relapsed/refractory patients, with acceptable toxicities [68]. The PR was achieved in leiomyosarcoma, rhabdomyosarcoma, neuroblastoma [69], undifferentiated sarcoma, and Wilms' tumor (Table 2). As a single, independent experience, Rosoff and Bayliff [70] administered irinotecan 50 mg/m<sup>2</sup>/day for 5 days every 3-4 weeks in 2 patients with desmoplastic round blue cell tumors and saw significant responses. As far as the treatment of

childhood solid tumors is concerned, at present irinotecan appears to be promising in the treatment of childhood solid tumors such as rhabdomyosarcoma, neuroblastoma, and desmoplastic round blue cell tumor [55,58,66,68-70].

#### ORAL ADMINISTRATION OF TOPOTECAN AND IRINOTECAN

The efficacy of the protracted oral administration of topotecan and irinotecan has been well established *in vivo* [15,50,71]. While previous studies [72-74] evaluated the safety and disposition of oral topotecan in adults, the oral administration of topotecan in children has also recently been evaluated in a phase I study [75]. In addition, Daw *et al.* found that the MTD was 1.8 mg/m<sup>2</sup>/day on a daily  $\times 5 \times 2$  schedule, which was higher than the MTD for adults [74], and that the disease stabilized in 9 of 19 assessable patients for 1.5 to 6 months [75]. The dose-limiting factors were myelosuppression and diarrhea in this pediatric cohort receiving oral topotecan [75]. However, oral administration of irinotecan has not yet undergone phase I trials in pediatric patients with malignant solid tumors.

#### TOPOISOMERASE I INHIBITORS GIVEN IN COMBINATION WITH OTHER CHEMOTHERAPEUTIC AGENTS

It has been suggested that topoisomerase I inhibitors should be investigated in combination with other chemotherapeutic agents [20]. There is evidence of a lack of cross-resistance between camptothecin analogues and other anticancer drugs [76]. Furthermore, several preclinical studies showed that the administration of topoisomerase I inhibitors with alkylators, platinum compounds, topoisomerase II inhibitors, and antimicrotubule agents produces additive or synergic antitumor activity [77,78]. However, an antagonistic rather than a synergic effect may also be produced by camptothecin analogs when combined with certain drugs [79,80]. The efficacy of drug combinations depends on the schedule of administration and on the choice of drugs. Several adult and pediatric clinical

**Table 2. Results of Phase II Administration\* of Irinotecan Studied by the Authors' Group [68]**

Disease	No. of Patients	PR	SD**	SD	PD
Leiomyosarcoma	1	1			
Neuroblastoma	6	1	2	2	1
PNET	1				1
Undifferentiated sarcoma	1	1			
Wilms' tumor	2	1			1
Rhabdomyosarcoma	2	1			1
Total	13	5	2	2	4

\*, irinotecan 180 mg/m<sup>2</sup>/day for 3 consecutive days, repeated once after 25 days off; PR, partial response; SD\*\*, stable disease (SD) but with transient decrease in tumor marker levels; PD, progressive disease; PNET, primitive neuroectodermal tumor.

studies (phase I and phase II) of multiagent therapy including topotecan and irinotecan were reviewed by Rodriques-Galindo *et al.* [20].

Noda and associates [81] recently compared clinical results of patients treated with irinotecan plus cisplatin and those treated with etoposide plus cisplatin for extensive small-cell lung cancer. At the time when the 154 patients were enrolled, the median survival was 12.8 months in the irinotecan / cisplatin group and 9.4 months in the etoposide / cisplatin group ( $p=0.002$  by the unadjusted log-rank test). At 2 years, the proportion of patients surviving was 19.5% in the irinotecan/ cisplatin group and 5.2% in the etoposide / cisplatin group [81]. Severe or life-threatening myelosuppression was more frequent in the etoposide-/ cisplatin group than in the irinotecan/ cisplatin group, and severe or life-threatening diarrhea was more frequent in the irinotecan/cisplatin group than in the etoposide / cisplatin group.

In children, cyclophosphamide plus topotecan was administered to patients with recurrent or refractory solid tumors [82], and the combination of cyclophosphamide and topotecan was found to be active against rhabdomyosarcoma, neuroblastoma, and Ewing's sarcoma [82]. Similarly, a window trial with topotecan and cyclophosphamide carried out in children with newly diagnosed metastatic rhabdomyosarcoma [41] found that topotecan after cyclophosphamide is active against newly diagnosed rhabdomyosarcoma. However, survival rates remained disappointing for children with metastatic rhabdomyosarcoma at diagnosis [41]. The problems related to the combined use of topotecan with cyclophosphamide was extensively reviewed [41].

There are many combinations of topoisomerase I inhibitors with other chemotherapeutic agents in adults [20], but a combination of topotecan/irinotecan with the alkylating agent cyclophosphamide has been employed more frequently in children [20,41,82,83]. Kushner and his coworkers [83] used such a combination in the treatment of resistant neuroblastoma.

### POLYMORPHISMS OF THE URIDINE-DIPHOSPHATE-GLUCURONOSYLTRANSFERASE GENE AND IRINOTECAN TOXICITY

Irinotecan unexpectedly causes severe toxicity in the form of leukopenia or diarrhea, presumably because it is metabolized to form active SN-38, which is further conjugated and detoxified by the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzyme [84]. Genetic polymorphisms of UGT1A1 would affect the interindividual variation in irinotecan toxicity via the alteration of the bioavailability of SN-38. Ando and co-workers studied the relationship between multiple variant genotypes (UGT1A1\*28 in promoter and UGT1A1\*6, UGT1A1\*27, UGT1A1\*29, and UGT1A1\*7 in the coding region) and severe toxicity of grade 4 leukopenia and/or grade 3 or 4 diarrhea in patients with various cancers [84]. Of 26 patients with severe toxicity, the genotypes of UGT1A1\*28 were homozygous in 4 (15%) and heterozygous in 8 (31%), whereas 3 (3%) were homozygous and 10 (11%) heterozygous among the 92 patients without severe toxicity. Multivariate analysis suggested that the genotype either heterozygous or homozygous for UGT1A1\*28 would be a significant risk factor for severe irinotecan toxicity [84].

Font *et al.* [85] similarly investigated the relationship with toxicity and the antitumor activity in patients with non-small cell lung cancer, but found no differences in toxicity based on UGT1A1 polymorphism. They also concluded that the tendency for a better prognosis in patients carrying the variant genotype 6/7 and 7/7 of the UGT1A1 gene requires further validation [85].

### SUMMARY

The advent of topotecan and irinotecan in the treatment of childhood solid tumors may be comparable to that of cisplatin, which occurred some 20 years ago. Topotecan was utilized first, and subsequently irinotecan has been employed pre-clinically and clinically. Unfortunately, these two agents were not fully investigated in phase I and II trials. The clinical application of such new agents requires the

completion of well-designed phase III randomized trials. It is to be hoped that researchers worldwide will investigate a variety of administration schedules and not simply mimic what others have done, so that clinically important agents will not be missed. The future of topotecan and irinotecan administration is not yet resolved.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

#### REFERENCES

- [1] Matthay KK, Villablanca JG, Seeger RC, *et al.* Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999; 341: 1165-73.
- [2] Kawa K, Ohnuma N, Kaneko M, *et al.* Long-term survivors of advanced neuroblastoma with MYCN amplification: A report of 19 patients surviving disease-free for more than 66 months. *J Clin Oncol* 1999; 17: 3216-20.
- [3] Raney RB, Anderson JR, Barr FR, *et al.* Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: A selective review of Intergroup Rhabdomyosarcoma Study Group experience and rationale for Intergroup Rhabdomyosarcoma Study V. *J Pediatr Hematol Oncol* 2001; 23: 215-20.
- [4] Stevens MCG. Rhabdomyosarcoma. In: Voûte PA, Kalifa C, Barrett A, eds. *Cancer in Children: Clinical Management*. Oxford, Oxford University Press, 1998; 193-215.
- [5] Makino S, Kashii A, Kanazawa K, Tsuchida Y. Effects of newly introduced chemotherapeutic agents on a cytogenetically highly malignant neuroblastoma, xenotransplanted in nude mice. *J Pediatr Surg* 1993; 28: 612-6.
- [6] Choi SH, Tsuchida Y, Kamii Y, Yang HW, Komuro H, Makino S. Effects of paclitaxel, fotemustine, irinotecan, mitomycin C, ifosfamide and bleomycin on a highly malignant xenotransplanted neuroblastoma. *Cancer J* 1996; 9: 323-8.
- [7] Ikeda H, Tsuchida Y, Wu JG, *et al.* Antitumor effects of fotemustine and busulfan against a human neuroblastoma xenograft. *Oncol Rep* 2000; 7: 1265-8.
- [8] Gottlieb JA, Luce J. Treatment of malignant melanoma with camptothecin (NSC-100880). *Cancer Chemother Rep* 1972; 56: 103-5.
- [9] Kingsbury WD, Boehm JC, Jakas DR, *et al.* Synthesis of water soluble (aminoalkyl) camptothecin analogues: Inhibition of topoisomerase I and antitumor activity. *J Med Chem* 1991; 34: 98-107.
- [10] Houghton PJ, Cheshire PJ, Myers L, Stewart CF, Synold TW, Houghton JA. Evaluation of 9-dimethylaminomethyl-10-hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. *Cancer Chemother Pharmacol* 1992; 31: 229-39.
- [11] Kaneda N, Nagata H, Furuta T, Yokokura T. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse. *Cancer Res* 1990; 50: 1715-20.
- [12] Pratt CB, Stewart C, Santana VM, *et al.* Phase I study of topotecan for pediatric patients with malignant solid tumors. *J Clin Oncol* 1994; 12: 539-43.
- [13] Vassal G, Pondarre C, Boland I, *et al.* Preclinical development of camptothecin derivatives and clinical trials in pediatric oncology. *Biochimie* 1998; 80: 271-80.
- [14] Tanizawa A, Fujimori A, Fujimori Y, Pommier Y. Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. *J Natl Cancer Inst* 1994; 86: 836-42.
- [15] Houghton PJ, Cheshire PJ, Hallman JD, *et al.* Efficacy of topoisomerase I inhibitors, topotecan and irinotecan, administered at low doses in protracted schedules to mice bearing xenografts of human tumors. *Cancer Chemother Pharmacol* 1995; 36: 393-403.
- [16] Pawlik CA, Houghton PJ, Stewart CF, Cheshire PJ, Richmond LB, Danks MK. Effective schedules of exposure of medulloblastoma and rhabdomyosarcoma xenografts to topotecan correlates with *in vitro* assays. *Clin Cancer Res* 1998; 4: 1995-2002.
- [17] Zamboni WC, Stewart CF, Thompson J, *et al.* Relationship between topotecan systemic exposure and tumor response in human neuroblastoma xenografts. *J Natl Cancer Inst* 1998; 90: 505-511.
- [18] Rowinsky EK, Verwij J. Review of phase I clinical studies with topotecan. *Semin Oncol* 1997; 24: S20-3-S20-10.
- [19] Dennis MJ, Beijnen JH, Grochow LB, van Warmerdam LJ. An overview of the clinical pharmacology of topotecan. *Semin Oncol* 1997; 24: S5-12-S5-18.
- [20] Rodriguez-Galindo C, Radomski K, Stewart CF, Furman W, Santana VM, Houghton PJ. Clinical use of topoisomerase I inhibitors in anticancer treatment. *Med Pediatr Oncol* 2000; 35: 385-402.
- [21] Furman WL, Baker SD, Pratt CB, Rivera GK, Evans WE, Stewart CF. Escalating systemic exposure of continuous infusion topotecan in children with recurrent acute leukemia. *J Clin Oncol* 1996; 14: 1504-11.
- [22] Tubergen DG, Stewart CF, Pratt CB, *et al.* Phase I trial and pharmacokinetic (PK) and pharmacodynamics (PD) study of topotecan using a five-day course in children with refractory solid tumors: A Pediatric Oncology Group study. *J Pediatr Hematol Oncol* 1996; 18: 352-61.
- [23] Zamboni WC, Santana VM, Gajjar A, *et al.* Pharmacokinetically guided dose adjustment reduces variability in topotecan (TPT) systemic exposure in children with solid tumors. *Proc Annu Meet Am Soc Clin Oncol* 1997; 16: A717.
- [24] Santana VM, Zamboni WC, Gajjar A, *et al.* Pharmacokinetically guided use of topotecan (TPT), given (daily  $\times$  5)  $\times$  2, in children with relapsed solid tumors. *Proc Annu Meet Am Soc Clin Oncol* 1997; 16: A1839.
- [25] Hoskins P, Eisenhauer E, Beare S, *et al.* Randomized phase II study of two schedules of topotecan in previously treated patients with ovarian cancer: A National Cancer Institute of Canada Clinical Trials Group study. *J Clin Oncol* 1998; 16: 2233-7.
- [26] Creemers GJ, Bolis G, Gore M, *et al.* Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: Results of a large European phase II study. *J Clin Oncol* 1996; 14: 3056-61.
- [27] Kudelka AP, Tresukosol D, Edwards CL, *et al.* Phase II study of intravenous topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma. *J Clin Oncol* 1996; 14: 1552-7.
- [28] Armstrong D, Rowinsky E, Donehower R, *et al.* A phase II trial of topotecan as salvage therapy in epithelial ovarian cancer. *Proc Annu Meet Am Soc Clin Oncol* 1995; 14: A769.
- [29] Ten Bokkel Huinik WW, Gore M, Bolis G, *et al.* A phase II trial of topotecan for the treatment of relapsed advanced ovarian carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 1996; 15: A768.
- [30] Carmichael J, Gordon A, Malfetano J, *et al.* Topotecan, a new active drug, vs. paclitaxel in advanced epithelial ovarian carcinoma: International Topotecan Study Group Trial. *Proc Annu Meet Am Soc Clin Oncol* 1996; 15: A765.
- [31] Gordon A, Bookman M, Malstrom H, *et al.* Efficacy of topotecan in advanced epithelial ovarian cancer after failure of platinum and paclitaxel: International Topotecan Study Group Trial. *Proc Annu Meet Am Soc Clin Oncol* 1996; 15: A763.
- [32] Ardizzoni A, Hansen H, Dombrowsky P, *et al.* Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: A phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. *J Clin Oncol* 1997; 15: 2090-6.
- [33] Perez-Soler R, Glisson BS, Lee JS, *et al.* Treatment of patients with small-cell lung cancer refractory to etoposide and cisplatin with topoisomerase I poison topotecan. *J Clin Oncol* 1996; 14: 2785-90.

- [34] Lynch TJ Jr, Kalish L, Strauss G, *et al.* Phase II study of topotecan in metastatic non-small-cell lung cancer. *J Clin Oncol* 1994; 12: 347–52.
- [35] Weitz JJ, Marschke RF Jr, Sloan JA, *et al.* A randomized phase II trial of two schedules of topotecan for the treatment of advanced stage non-small cell lung cancer. *Lung Cancer* 2000; 28: 157–62.
- [36] Perez-Soler R, Fossella FV, Glisson BS, *et al.* Phase II study of topotecan in patients with advanced non-small-cell lung cancer previously untreated with chemotherapy. *J Clin Oncol* 1996; 14: 503–13.
- [37] Beran M, Kantarjian H. Topotecan in the treatment of hematologic malignancies. *Semin Hematol* 1998; 35: 26–31.
- [38] Blaney SM, Needle MN, Gillespie A, *et al.* Phase II trial of topotecan administered as a 72-hour continuous infusion in children with refractory solid tumors: A collaborative Pediatric Branch, National Cancer Institute, and Children's Cancer Group Study. *Clin Cancer Res* 1998; 4: 357–60.
- [39] Nitschke R, Parkhurst J, Sullivan J, Harris MB, Bernstein M, Pratt C. Topotecan in pediatric patients with recurrent and progressive solid tumors: A Pediatric Oncology Group phase II study. *J Pediatr Hematol Oncol* 1998; 20: 315–8.
- [40] Kretschmar C, Kletzel M, Murray K, *et al.* Upfront phase II therapy with taxol (Txl) and topotecan (Topo) in untreated children with disseminated (INSS stage 4) neuroblastoma: A Pediatric Oncology Group (POG) study. *Med Pediatr Oncol* 1995; 25: 243a.
- [41] Walterhouse DO, Lyden ER, Breitfeld PP, Qualman SJ, Wharam MD, Meyer WH. Efficacy of topotecan and cyclophosphamide given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: A Children's Oncology Group study. *J Clin Oncol* 2004; 22: 1398–403.
- [42] Kunimoto T, Nitta K, Tanaka T, *et al.* Anti-tumor activity of 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-1-carbonyl-camptothecin, a novel water soluble derivative of camptothecin, against murine tumors. *Cancer Res* 1987; 47: 5944–7.
- [43] Matsuzaki T, Yokokura T, Mutai M, Tsuruo T. Inhibition of spontaneous and experimental metastasis by a new derivative of camptothecin, CPT-11, in mice. *Cancer Chemother Pharmacol* 1988; 21: 308–12.
- [44] Bissery MC, Mathieu-Boue A, Lavelle F. Preclinical evaluation of CPT-11 *in vitro* and *in vivo*. *Proc Am Assoc Cancer Res* 1991; 33: A2389.
- [45] Bissery MC, Mathieu-Boue A, Lavelle F. Experimental activity of CPT-11 *in vitro* and *in vivo*. *Ann Oncol* 1992; 3 [Suppl 1]: A093.
- [46] Kawato Y, Furuta T, Aonuma M, Yasuoka M, Yokokura T, Matsumoto K. Antitumor activity of a camptothecin derivative, CPT-11, against human tumor xenografts in nude mice. *Cancer Chemother Pharmacol* 1991; 28: 192–8.
- [47] Houghton PJ, Cheshire PJ, Hallman JC, Bissery MC, Mathieu-Boue A, Houghton JA. Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-(4-[1-piperidino]-1-piperidino)-1-carbonyl-camptothecin against human tumor xenografts: Lack of cross resistance *in vivo* in tumors with acquired resistance to the topoisomerase inhibitor 9-dimethylaminomethyl-10-hydroxycamptothecin. *Cancer Res* 1993; 53: 2823–9.
- [48] Kamii Y, Tsuchida Y, Yokomori K. Effects of CPT-11 on a human rhabdomyosarcoma in nude mice and in culture. *Int J Pediatr Hematol Oncol* 1996; 3: 201–5.
- [49] Thompson J, Zamboni WC, Cheshire PJ, *et al.* Efficacy of systemic administration of irinotecan against neuroblastoma xenografts. *Clin Cancer Res* 1997; 3: 423–431.
- [50] Thompson J, Zamboni WC, Cheshire PJ, *et al.* Efficacy of oral administration of irinotecan against neuroblastoma xenografts. *Anticancer Res* 1997; 8: 313–22.
- [51] Komuro H, Li P, Tsuchida Y, *et al.* Effects of CPT-11 (a unique DNA topoisomerase I inhibitor) on a highly malignant xenotransplanted neuroblastoma. *Med Pediatr Oncol* 1994; 23: 487–92.
- [52] Vassal G, Bolando I, Santos A, *et al.* Potent therapeutic activity of irinotecan (CPT-11) and its schedule-dependency in medulloblastoma xenografts in nude mice. *Int J Cancer* 1997; 73: 156–67.
- [53] Masuda N, Kudoh S, Fukuoka M. Irinotecan (CPT-11): Pharmacology and clinical application. *Crit Rev Oncol Hematol* 1996; 24: 3–26.
- [54] O'Reilly S, Rowinsky EK. The clinical status of irinotecan (CPT-11), a water soluble camptothecin analogue. *Crit Rev Oncol Hematol* 1996; 24: 47–70.
- [55] Furman WL, Stewart CF, Poquette CA, *et al.* Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children. *J Clin Oncol* 1999; 17: 1815–24.
- [56] Blaney S, Berg SL, Pratt C, *et al.* Phase I study of irinotecan in pediatric patients: a Pediatric Oncology Group study. *Clin Cancer Res* 2001; 7: 32–7.
- [57] Vassal G, Doz F, Frappaz D, *et al.* A phase I study of irinotecan as a 3-week schedule in children with refractory or recurrent solid tumors. *J Clin Oncol* 2003; 21: 3844–52.
- [58] Mugishima H, Matsunaga T, Yagi K, *et al.* Phase I study of irinotecan in pediatric patients with malignant solid tumors. *J Pediatr Hematol Oncol* 2002; 24: 94–100.
- [59] Ohno R, Okada K, Masaoka T, *et al.* An early phase II study of CPT-11, A new derivative of camptothecin, for the treatment of leukemia and lymphoma. *J Clin Oncol* 1990; 8: 1907–12.
- [60] Fukutani K, Wakui A, Nakao M, *et al.* Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. *Jpn J Cancer Chemother* 1994; 21: 1033–8.
- [61] Masuda N, Fukuoka M, Kusunoki Y, *et al.* CPT-11: A new derivative of camptothecin for the treatment of refractory or relapsed small cell lung cancer. *J Clin Oncol* 1992; 10: 1225–9.
- [62] Fukuoka M, Niitani H, Suzuki A, *et al.* A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small cell lung cancer. *J Clin Oncol* 1992; 10: 16–20.
- [63] Takeuchi S, Takamizawa H, Takeda Y, *et al.* Clinical study of CPT-11, a camptothecin derivative, in gynecological malignancy. *Proc Am Soc Clin Oncol* 1990; 10: 189.
- [64] Moertel CG, Schut AJ, Reitemeier RJ, Hahn RG. Phase II study of camptothecin in the treatment of advanced gastro-intestinal cancer. *Cancer Chemother Rep* 1992; 56: 95–101.
- [65] Shimada Y, Yoshino M, Wakui A, *et al.* Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. *J Clin Oncol* 1993; 11: 909–13.
- [66] Cosetti M, Wexler LH, Calleja E, *et al.* Irinotecan for pediatric solid tumors: The Memorial Sloan-Kettering experience. *J Pediatr Hematol Oncol* 2002; 24: 101–5.
- [67] Vassal G, Doz F, Frappaz D, *et al.* A phase II study of irinotecan (CPT-11) in children with relapsed or refractory neuroblastoma. *Med Pediatr Oncol* 2002; 39: 257.
- [68] Shitara T, Shimada A, Hanada R, *et al.* The use of irinotecan 160–180 mg/m<sup>2</sup>/day for 3 days in children with relapsed solid tumors: An early phase II study. *J Pediatr Surg* (submitted).
- [69] Shitara T, Shimada A, Tsuchida Y, Suzuki N, Toki F, Kuroiwa M. Successful clinical response to irinotecan in relapsed neuroblastoma. *Med Pediatr Oncol* 2003; 40: 126–8.
- [70] Rosoff PM, Bayliff S. Successful clinical response to irinotecan in desmoplastic round blue cell tumor. *Med Pediatr Oncol* 1999; 33: 500–3.
- [71] Choi SH, Yang HW, Tsuchida Y. Oral versus intraperitoneal administration of irinotecan in the treatment of human neuroblastoma in nude mice. *Cancer Lett* 1998; 124: 15–21.
- [72] Gerrits CJ, Burris H, Schellens JH, *et al.* Five days of oral topotecan (Hycamtin): A phase I and pharmacological study in adult patients with solid tumors. *Eur J Cancer* 1998; 34: 1030–5.
- [73] Creemers GJ, Gerrits CJ, Eckard JR, *et al.* Phase I and pharmacological study of oral topotecan administered twice daily for 21 days to adult patients with solid tumors. *J Clin Oncol* 1997; 15: 1087–93.
- [74] Gerrits CJ, Burris H, Schellens JH, *et al.* Oral topotecan given once or twice daily for ten days: A phase I pharmacology study in adult patients with solid tumors. *Clin Cancer Res* 1998; 4: 1153–8.
- [75] Daw NC, Santana VM, Iacomio LC, *et al.* Phase I and pharmacokinetic study of topotecan administered orally once daily for 5 days for 2 consecutive weeks to pediatric patients with refractory solid tumors. *J Clin Oncol* 2004; 22: 829–37.
- [76] Mattern MR, Hofmann GA, Polsky RM, Funk LR, McCabe FL, Johnson RK. *In vitro* and *in vivo* effects of clinically important camptothecin analogues on multidrug-resistant cells. *Oncol Res* 1993; 5: 467–74.
- [77] Chou TC, Motzer RJ, Tong Y, Bosl GJ. Computerized quantitation of synergic and antagonism of taxol, topotecan, and cisplatin against human teratocarcinoma cell growth: A rational approach to clinical protocol design. *J Natl Cancer Inst* 1994; 86: 1517–24.
- [78] Kaufmann SH, Peerebom D, Buckwater CA, *et al.* Cytotoxic effects of topotecan combined with various anticancer agents in human cancer cell lines. *J Natl Cancer Inst* 1996; 88: 734–41.

- [79] Cheng MF, Chatterjee S, Berger NA. Schedule dependent cytotoxicity of topotecan alone and in combination chemotherapy regimens. *Oncol Res* 1994; 6: 269–79.
- [80] Kaufmann SH. Antagonism between camptothecin and topoisomerase II-directed chemotherapeutic agents in a human leukemia cell line. *Cancer Res* 1991; 51: 1129–36.
- [81] Noda K, Nishiwaki Y, Kawahara M, *et al.* Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; 346: 85–91.
- [82] Saylor RL III, Stine KC, Sullivan J, *et al.* Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: A Pediatric Oncology Group phase II study. *J Clin Oncol* 2001; 19: 3463–69.
- [83] Kushner BH, Kramer K, Modak S, Cheung NK. Camptothecin analogs (irinotecan or topotecan) plus high-dose cyclophosphamide as preparative regimens for antibody-based immunotherapy in resistant neuroblastoma. *Clin Cancer Res* 2004; 10: 84–7.
- [84] Ando Y, Saka H, Ando M, *et al.* Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: A pharmacogenetic analysis. *Cancer Res* 2000; 60: 6921–6.
- [85] Font A, Sanchez JM, Taron M, *et al.* Weekly regimen of irinotecan/docetaxel in previously treated non-small cell lung cancer patients and correlation with uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) polymorphism. *Invest New Drugs* 2003; 21: 435–43.