Cancer Chemother Pharmacol (2001) 47: 89–93
DOI 10.1007/s002800000224

CLINICAL TRIAL REPORT

**Jon D. Herrington · Jose A. Figueroa
Mark N. Kirstein · William C. Zamboni
Clinton F. Stewart**

# Effect of hemodialysis on topotecan disposition in a patient with severe renal dysfunction

Received: 21 June 2000 / Accepted: 17 October 2000 / Published online: 22 November 2000


**Abstract** The pharmacokinetics of topotecan have been extensively studied in patients with normal renal function and there is one study of patients with mild to moderate renal insufficiency. However, the effect of hemodialysis on topotecan disposition has not been reported. The objective of this study was to characterize the disposition of topotecan in a patient with severe renal insufficiency receiving hemodialysis. Topotecan lactone disposition was characterized in a patient on and off hemodialysis. The topotecan lactone clearance determined after administration of topotecan alone and with hemodialysis was 5.3 l/h per $m^2$ vs 20.1 l/h per $m^2$, respectively. At 30 min after the completion of hemodialysis, the topotecan plasma concentration obtained was greater than that measured at the end of hemodialysis (i.e. 8.0 ng/ml vs 4.9 ng/ml), suggesting a rebound effect. The topotecan terminal half-life off dialysis was 13.6 h, compared with an apparent half-life determined during hemodialysis of 3.0 h. These results demonstrate that topotecan plasma clearance while on hemodialysis increased approximately fourfold. Hemodialysis may be an effective systemic clearance process for topotecan and should be considered in selected clinical situations (e.g. inadvertent overdose, severe renal dysfunction).

**Key words** Pharmacokinetics · Topoisomerase I inhibitors · Kidney failure · Hemodialysis

Supported in part by USPHS Awards CA223099 and by American, Lebanese, Syrian Associated Charities (ALSAC).

J. D. Herrington
Department of Pharmacy, Scott & White Memorial Hospital, Temple, TX 76508, USA

J. D. Herrington
Department of Medicine,
Texas A&M University College of Medicine, Temple, TX, USA

J. A. Figueroa
Clinical Research Division, Joe Arrington Cancer Center, Lubbock, TX 79410, USA

M. N. Kirstein · C. F. Stewart (✉)
Department of Pharmaceutical Sciences,
St. Jude Children's Research Hospital,
332 N. Lauderdale, Memphis, TN 38105, USA
Tel.: +1-901-4953665; Fax: +1-901-5256869

W. C. Zamboni
Program for Molecular Therapeutics and Drug Discovery,
University of Pittsburgh Cancer Institute,
University of Pittsburgh, Pittsburgh, PA 15213, USA

W. C. Zamboni
Department of Pharmaceutical Sciences, School of Pharmacy,
University of Pittsburgh, Pittsburgh, PA, USA

W. C. Zamboni
Department of Medicine, School of Medicine,
University of Pittsburgh, Pittsburgh, PA, USA

## Introduction

Topotecan, a synthetic camptothecin analog that inhibits the enzyme topoisomerase I, has displayed significant activity against a wide variety of malignancies [11, 13, 14]. Renal excretion appears to be the primary route for topotecan elimination, with 26% to 68% of a topotecan dose recovered in the urine as total topotecan, the sum of topotecan lactone and hydroxy acid forms [6, 16, 18]. Since a significant amount of drug is eliminated via renal excretion, patients with renal impairment may be at increased risk of toxicity, including myelosuppression, diarrhea, fatigue, and rash [9]. The pharmacokinetics of topotecan was examined in patients with impaired renal function receiving topotecan as a 30-min infusion daily for 5 days every 3 weeks [8]. Based on the results of this study, the investigators recommended that in patients with moderate renal dysfunction, defined as a creatinine clearance of 20 to 39 ml/min, the topotecan dose is reduced by 50% (i.e. from the FDA approved dose of 1.5 to 0.75 mg/$m^2$ per day for 5 days every 3 weeks). To reduce the likelihood of additional toxicities in heavily pretreated patients with renal insufficiency, the investigators recommend that further dose reductions be considered.

In contrast to these observations, we have reported normal systemic exposure and renal clearance of topo-

tecan lactone in a pediatric patient with severe renal dysfunction (i.e. $^{Tc99m}$DTPA clearance 19 ml/min per $m^2$) [20]. Thus, the influence of severe renal dysfunction on topotecan disposition is unclear. The objectives of this study were to measure the topotecan disposition in a patient with severe renal dysfunction (i.e. creatinine clearance < 10 ml/min), and to characterize the effect of hemodialysis on topotecan disposition. This is the first study in which the effect of hemodialysis on the disposition of topotecan has been evaluated.

## Patient and methods

The study patient was a 58-year-old woman with advanced ovarian carcinoma. Her previous chemotherapy included 11 cycles of cyclophosphamide and carboplatin, 6 cycles of paclitaxel and carboplatin, and 3 cycles of vinorelbine. She subsequently presented with progressive ovarian carcinoma characterized by a CA125 level of 199.5 U/ml, and her primary physician chose to treat her with single-agent topotecan. The patient received two cycles of topotecan given as a 30-min infusion at a dose of 1.5 mg/$m^2$ per day for 5 days, and developed febrile neutropenia after each course despite growth factor support and prophylactic ciprofloxacin. With her third cycle, the topotecan dose was reduced to 1 mg/$m^2$ for 5 days. Her CA125 levels had declined to 60.7 U/ml. During this course, she experienced a colonic perforation that delayed further chemotherapy for almost 3 months. Approximately 1 month after her fourth cycle, she developed bilateral pleural effusions and oliguric renal failure (blood urea nitrogen 39 mg/dl and serum creatinine 9 mg/dl). Her renal failure was attributed to tumor obstruction that did not improve upon left percutaneous nephrostomy and ureteral stent placement. Therefore, the patient was placed on hemodialysis. Continuation of topotecan therapy was desired since the patient had had a clinical response defined by decreased ascites, omental caking, improved wellbeing, and a further decrease in CA125 levels to 53.2 U/ml.

Due to her severe renal failure (creatinine clearance < 10 ml/min), and the unknown effect of hemodialysis on topotecan disposition, we chose to empirically reduce the topotecan dosage based on the guidelines of O'Reilly et al. for patients receiving topotecan with renal dysfunction [8]. Moreover, this empirical dose reduction was supported by toxicities observed on previous cycles of topotecan therapy. For this fifth cycle of therapy, the topotecan dosage was reduced from 1 mg/$m^2$ administered as a 30-min infusion daily for 5 days to 1 mg/$m^2$ for 2 days, or a 60% reduction in the cumulative topotecan dose for the course. The topotecan doses were administered on days 1 and 3, with hemodialysis on days 2 and 4. Without the use of a hematopoietic growth factor, she developed grade 4 neutropenia (ANC nadir on day 14 of 144 cells/μl) lasting approximately 8 days; however, she did not develop febrile neutropenia. In addition, she developed grade 3 thrombocytopenia (platelet nadir on day 14 of 48,000 cells/μl) which lasted approximately 2 days.

The sixth cycle of topotecan was administered after the resolution of myelosuppression from the previous cycle of therapy on day 30. In order to determine the effect of hemodialysis on topotecan disposition, we performed extensive pharmacokinetic studies while the patient received topotecan both on and off hemodialysis. The proposed study was reviewed and approved by the Scott and White Memorial Hospital Institutional Review Board. During the sixth cycle, topotecan 1 mg/$m^2$ was administered as a 30-min infusion beginning at the start of the 4-h hemodialysis procedure. She was dialyzed on a Fresenius hemodialysis machine which utilized a Terumo 220 Cuperammonium Rayon H dialysis filter. The blood flow rate was 450 ml/min from a central venous catheter and the dialysate flow rate was 800 ml/min. The dialysate was composed of sodium 139 mmol/l, calcium 1.25 mmol/l, potassium 2 mmol/l, magnesium 0.5 mmol/l, chloride 105.5 mmol/l, acetate 4 mmol/l, bicarbonate 35 mmol/l, and dextrose 0.2 g/dl. The pH of the dialysate fluid was 5.2. On the day after hemodialysis, she received another topotecan 1 mg/$m^2$ 30-min infusion without hemodialysis.

The patient did experience grade 2 nausea and vomiting approximately 12 h after the second topotecan infusion. Without the use of hematopoietic growth factor, she developed grade 4 neutropenia (ANC nadir on day 10 was 192 cells/μl) lasting 13 days without fever, and grade 3 thrombocytopenia (platelet nadir on day 10 was $42\times10^3$ cells/μl) lasting approximately 2 days. No additional toxicities were noted.

### Sample collection, preparation, and HPLC analysis

The pharmacokinetics of topotecan were assessed while the patient was on and off hemodialysis. On the first day of her sixth cycle, topotecan was administered concomitantly with the start of hemodialysis. Venous blood and dialysate samples were obtained before, and 0.25, 0.5, 1, and 2 h after the end of the 30-min topotecan infusion, and an additional venous blood sample was drawn 0.5 h after the end of the 4-h hemodialysis. On the next day, the patient received topotecan without the hemodialysis procedure. Venous blood samples were obtained prior to the topotecan infusion, and at 0.25, 0.5, 5.75, and 30 h after the end of infusion. The samples were drawn from the port contralateral to the site used for topotecan administration.

At each time-point, 3 ml of blood and dialysate were collected and placed in a heparinized tube. Immediately after collection (i.e. within 2 min), the blood sample was centrifuged in a microfuge for 2 min at 10,000 rpm. The resultant plasma was isolated, and 200 μl of this plasma was added to 800 μl cold (–20 °C) methanol. The methanolic mixture was vortexed for 10 s, and then centrifuged for 2 min at 10,000 rpm. The supernatant was decanted into a screw-capped tube, and stored at –70 °C until analysis by HPLC. Topotecan lactone and total (sum of lactone and hydroxy acid) topotecan in plasma samples were measured by an isocratic HPLC assay with fluorescent detection [2, 3, 16, 17]. Topotecan was detected using a fluorescence detector (RF535; Shimadzu, Columbia, Md.) with excitation at 370 nm and emission at 520 nm. Calibration curves were constructed using single-donor human plasma or simulated dialysis fluid, as appropriate. The minimum detectable topotecan lactone concentration in plasma and dialysate was 0.25 ng/ml.

### Pharmacokinetic analysis

A two-compartment model was fitted using maximum likelihood estimation to topotecan lactone and total plasma concentrations (ADAPT II) [4]. For intravenous administration, model parameters estimated included the volume of the central compartment ($V_c$), elimination rate constant ($k_e$), and the intercompartmental rate constants ($k_{cp}$, $k_{pc}$). Using standard equations, systemic clearance (CL) and volume of distribution at steady-state ($Vd_{ss}$) were calculated from parameter estimates [5]. The area under the topotecan lactone concentration-time curve was calculated using the log trapezoidal method.

## Results

The topotecan pharmacokinetic parameters determined while on and off hemodialysis are summarized in Table 1. The topotecan lactone plasma concentration-time data after administration of topotecan alone and in combination with hemodialysis are presented in Fig. 1. The median ratio of lactone-to-total venous concentrations obtained while on and off hemodialysis was 0.81 (range 0.70 to 0.86) and 0.57 (0.50 to 0.82), respectively.

As shown in Fig. 2, the topotecan lactone concentrations measured in the dialysate fluid ranged from 0.45

**Table 1** Pharmacokinetic parameters of topotecan lactone determined for a patient with severe renal dysfunction while off hemodialysis and during hemodialysis. The details of the hemodialysis procedure are described in the Methods ($V_c$ volume of the central compartment, $k_e$ elimination rate constant, $t_{1/2\ \beta}$ elimination half-life $\beta$ phase, $CL$ topotecan clearance, $Vd_{ss}$ volume of distribution at steady-state, $AUC_{0\to\infty}$ area under the concentration-time curve to infinity)

| Parameter | No hemodialysis | Hemodialysis |
|---|---|---|
| $V_c$ (l/m$^2$) | 45.8 | 45.0 |
| $k_e$ (h$^{-1}$) | 0.12 | 0.45 |
| $t_{1/2\ \beta}$ (h) | 13.6 | 3.0 |
| CL (l/h/m$^2$) | 5.3 | 20.1 |
| $Vd_{ss}$ (l/m$^2$) | 94.1 | 80.9 |
| No. of points (last time-point) | 4 (30.5 h) | 5 (3.73 h) |
| $AUC_{0\to\infty}$ (ng · ml/h) | 168.3 | N/A |

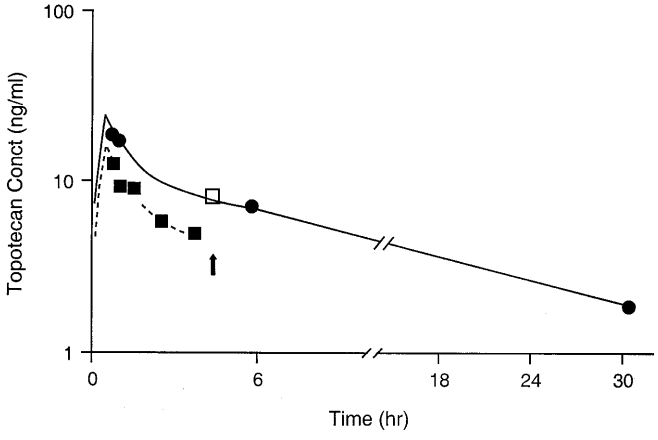


**Fig. 1** Effect of hemodialysis on topotecan plasma pharmacokinetics. The line represents the best-fit line for the topotecan lactone plasma concentration versus time data while off hemodialysis (*solid line* ●) and while receiving hemodialysis (*dashed line* ■). The arrow denotes the rebound effect for topotecan lactone (□)

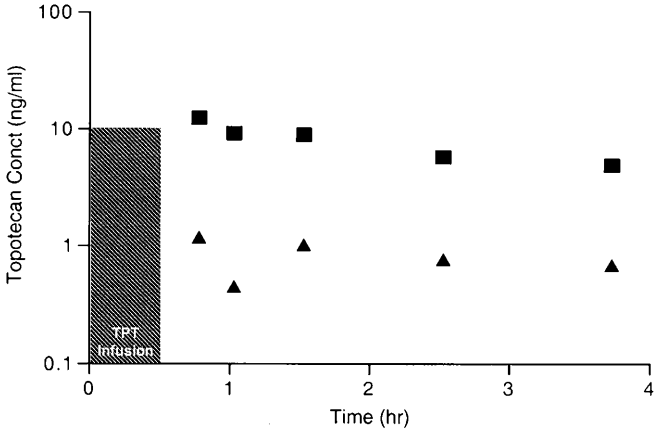


**Fig. 2** Topotecan disposition during hemodialysis (■ topotecan lactone plasma concentrations, ▲ topotecan lactone dialysate concentrations)

to 1.20 ng/ml, and these values were 5% to 14% of the concurrently measured plasma topotecan lactone concentrations. In contrast to the plasma lactone-to-total concentration ratio, that for dialysate was much lower with a median value of 0.30 (range 0.13 to 0.36), and no trend upward or downward was evident throughout the 4-h dialysis procedure.

The apparent topotecan half-life determined during the 4-h dialysis procedure was 3.0 h, compared with approximately 13.6 h off dialysis. The topotecan lactone clearance in this patient with severe renal dysfunction even in the absence of hemodialysis (i.e. 5.3 l/h per m$^2$) was approximately 20% that of patients with normal renal function (i.e. 23 to 33 l/h per m$^2$).

Although the topotecan lactone clearance was increased during the hemodialysis procedure, the topotecan plasma concentration obtained at 0.5 h after the completion of hemodialysis was greater than that measured at the end of hemodialysis (i.e. 8.0 ng/ml vs 4.9 ng/ml). Due to logistical considerations no further plasma samples were obtained, so we were unable to characterize the distribution of topotecan from the tissue compartment into the central compartment, or the postdialysis rebound effect [15].

## Discussion

Although the systemic and renal disposition of topotecan has been evaluated in prior studies, this is the first study in which the effect of hemodialysis on topotecan disposition in the presence of severe renal dysfunction has been evaluated. The topotecan lactone systemic clearance without hemodialysis was 5.3 l/h per m$^2$, indicating that removal of the drug occurred by nonrenal processes including metabolism or biliary elimination. Topotecan lactone clearance determined during the hemodialysis procedure was 20.1 l/h per m$^2$ or approximately 72% of the range of values reported for adult patients with normal renal function (range 23.2 to 33.6 l/h per m$^2$) [1, 7, 18, 19]. However, topotecan clearance by hemodialysis may not be as complete as suggested by the systemic clearance calculated during the 4-h hemodialysis procedure due to the potential for rebound in plasma topotecan lactone concentrations after hemodialysis.

Topotecan contains the camptothecin pentacyclic structure with a lactone (closed ring) moiety in the E ring. This lactone is essential for cytotoxicity, and can undergo a rapid and reversible hydrolysis to the inactive ring-open or hydroxy acid form [12]. In this patient, we observed a wide range of lactone-to-total topotecan ratios for plasma and dialysate samples during hemodialysis. A slightly higher range of lactone to total ratios was obtained during hemodialysis, which might be attributed to the acid pH of the dialysate fluid. This higher lactone to total ratio observed during hemodialysis has possible clinical implications in that it is possible that the more water-soluble hydroxy acid form of topotecan was preferentially removed during hemodialysis.

The extent to which any systemic drug concentration is affected by hemodialysis is determined by the phys-

icochemical properties of the drug, including molecular weight, water solubility, plasma protein and tissue binding. Topotecan has a relatively low molecular weight (i.e. 421 g/mol) that should allow passage through the hemodialysis membrane. Second, topotecan was originally synthesized from the parent molecule camptothecin to provide greater water solubility [10], which should enhance the likelihood of removal by hemodialysis. Finally, since a large percentage of topotecan is unbound (approximately 79%), a large fraction of the drug is available for removal by hemodialysis [7]. However, the steady-state volume of distribution reported for topotecan ranges from about 25 to 472 l/m$^2$, indicating extensive binding to tissue components [7, 17]. This may help explain the rebound effect we noted in the sample obtained after the end of the hemodialysis procedure.

Few studies have addressed the processes by which topotecan is handled by the kidney. Investigators have assumed that topotecan undergoes glomerular filtration, but more recent studies by Zamboni et al. suggest that topotecan undergoes anionic renal tubular secretion [21]. They evaluated the disposition of topotecan alone, and when coadministered with probenecid in mice. There was decreased topotecan lactone, and total systemic and renal clearance. Therefore, it is possible that a patient with a decreased glomerular filtration rate may not require topotecan dosage reduction due to the possible presence of an intact tubular secretory pathway. This is clinically relevant for topotecan based on the steep drug exposure-response relationship demonstrated in preclinical and clinical studies [22]. An increase in drug exposure of as little as twofold has been associated with increased toxicity, whereas a twofold decrease in topotecan systemic exposure may lead to a loss of antitumor activity [22]. Moreover, the fact that topotecan undergoes renal tubular secretion also makes it likely that interactions occur with other drugs that are handled similarly by the kidney (e.g. trimethoprim, methotrexate).

As discussed above, this was the first study in which the effect of hemodialysis on topotecan disposition has been evaluated. We were limited in the sampling strategy by patient logistics and clinical considerations. As a result, we were unable to wait three to five alfa half-lives after topotecan administration to allow for adequate distribution. By administering topotecan and starting the hemodialysis at the same time, our clearance may be overestimated, reflecting mainly the distribution phase of topotecan. However, topotecan has a very rapid alfa half-life (about 3 min), so this effect may be minimal.

O'Reilly et al. suggest that the topotecan dosage should be reduced by 50% to 75% in patients with severe renal dysfunction [8]. The results of our study demonstrate that topotecan plasma clearance while on hemodialysis increased almost fourfold (i.e. 20.1 l/h per m$^2$ on hemodialysis vs 5.3 l/h per m$^2$ off hemodialysis). The topotecan systemic clearance observed while this patient was on hemodialysis approaches clearance values observed in patients with normal renal function. In fact, the amount of total drug removed by hemodialysis as estimated by a mass balance approach was approximately 60% of the total dose. Even though a rebound in plasma topotecan concentrations was observed after hemodialysis, this procedure may be an effective systemic clearance process for topotecan for patients with severe renal dysfunction, and should be considered in selected clinical situations (e.g. inadvertent overdose).

**Acknowledgements** The authors thank Ima Garcia, Jo Ann Culpepper, Suzan K. Hanna, and Audrey K. Smith for their excellent technical support.

## References

1. Abbruzzese JL, Madden T, Sugarman SM, Ellis AL, Loughlin S, Hess KR, Newman RA, Zwelling LA, Raber MN (1996) Phase I clinical and plasma and cellular pharmacological study of topotecan without and with granulocyte colony-stimulating factor. Clin Cancer Res 2: 1489
2. Baker SD, Heideman RL, Crom WR, Kuttesch JF, Gajjar A, Stewart CF (1996) Cerebrospinal fluid pharmacokinetics and penetration of continuous infusion topotecan in children with central nervous system tumors. Cancer Chemother Pharmacol 37: 195
3. Beijnen JH, Smith BR, Keijer WJ, Van Gijn R, Huinink WW, Vlasveld LT, Rodenhuis S, Underberg WJM (1990) High-performance liquid chromatographic analysis of the new antitumour drug SK&F 104864-A (NSC 609699) in plasma. J Pharm Biomed Anal 8: 789
4. D'Argenio DZ, Schumitzky A (1990) ADAPT II user's guide, 1st edn. Biomedical Simulations Resource, USC, Los Angeles
5. Gibaldi M, Perrier D (1982) Pharmacokinetics, 2nd edn. Marcel Dekker, New York
6. Grochow LB, Rowinsky EK, Johnson R, Ludeman S, Kaufmann SH, McCabe FL, Hurowitz L, DeLisa A, Donehower RC, et al (1992) Pharmacokinetics and pharmacodynamics of topotecan in patients with advanced cancer. Drug Metab Dispos 20: 706
7. Herben VM, ten Bokkel Huinink WW, Beijnen JH (1996) Clinical pharmacokinetics of topotecan. Clin Pharmacokinet 31: 85
8. O'Reilly S, Rowinsky EK, Slichenmeyer W, Donehower RC, Forastiere AA, Ettinger DS, Chen TL, Sartorius S, Grochow LB (1996) Phase I and pharmacologic study of topotecan in patients with impaired renal function. J Clin Oncol 14: 3062
9. O'Reilly S, Armstrong DK, Grochow LB (1997) Life-threatening myelosuppression in patients with occult renal impairment receiving topotecan. Gynecol Oncol 67: 329
10. Potmesil M (1994) Camptothecins: from bench research to hospital wards. Cancer Res 54: 1431
11. Pratt CB, Stewart CF, Santana VM, Bowman L, Furman W, Ochs J, Marina N, Kuttesch JF, Heideman R, Sandlund JT, Avery L, Meyer WH (1994) Phase I study of topotecan for pediatric patients with malignant solid tumors. J Clin Oncol 12: 539
12. Redinbo MR, Stewart L, Kuhn P, Champoux JJ, Hol WGJ (1998) Crystal structures of human topoisomerase I in covalent and noncovalent complexes with DNA. Science 279: 1504
13. Rowinsky EK, Grochow LB, Hendricks CB, Ettinger DS, Forastiere AA, Hurowitz LA, McGuire WP, Sartorius SE, Lubejko BG, Kaufmann SH, et al (1992) Phase I and pharmacologic study of topotecan: a novel topoisomerase I inhibitor. J Clin Oncol 10: 647
14. Saltz L, Sirott M, Young C, Tong W, Niedzwiecki D, Tzy-Jyun Y, Tao Y, Trochanowski B, Wright P, Barbosa K, et al (1993) Phase I clinical and pharmacology study of topotecan given

daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor (published erratum appears in J Natl Cancer Inst 1993 85(21):1777). J Natl Cancer Inst 85: 1499
15. Spivey JM, Blum RA, Nix DE (1992) Mathematic modeling of drug disposition and postdialysis rebound in patients requiring hemodialysis. Pharmacotherapy 12: 201
16. Stewart CF, Baker SD, Heideman RL, Jones D, Crom WR, Pratt CB (1994) Clinical pharmacodynamics of continuous infusion topotecan in children: systemic exposure predicts hematologic toxicity. J Clin Oncol 12: 1946
17. Tubergen DG, Stewart CF, Pratt CB, Zamboni WC, Winick N, Santana VM, Dryer ZA, Kurtzberg J, Bell B, Grier H, Vietti TJ (1996) Phase I trial and pharmacokinetic (PK) and pharmacodynamics (PD) study of topotecan using a five-day course in children with refractory solid tumors: a Pediatric Oncology Group Study. J Pediatr Hematol Oncol 18: 352
18. van Warmerdam LJ, Verweij J, Schellens JH, Rosing H, Davies BE, de Boer-Dennert M, Maes RA, Beijnen JH (1995) Pharmacokinetics and pharmacodynamics of topotecan administered daily for 5 days every 3 weeks. Cancer Chemother Pharmacol 35: 237
19. Wall JG, Burris HA III, Von Hoff DD, Rodriguez G, Kneuper-Hall R, Shaffer D, O'Rourke T, Brown T, Weiss G, Clark G, McVea S, Brown J, Johnson R, Friedman C, Smith B, Mann WS, Kuhn J (1992) A phase I clinical and pharmacokinetic study of topoisomerase I inhibitor topotecan (SK&F 104864) given as an intravenous bolus every 21 days. Anticancer Drugs 3: 337
20. Zamboni WC, Heideman RL, Meyer WH, Gajjar AJ, Crom WR, Stewart CF (1996) Pharmacokinetics (PK) of topotecan in pediatric patients with normal and altered renal function. Proc Am Soc Clin Oncol 15: 371
21. Zamboni WC, Houghton PJ, Johnson RK, Hulstein JL, Crom WR, Cheshire PJ, Hanna SK, Richmond LB, Stewart CF (1998) Probenecid alters topotecan systemic and renal disposition by inhibiting tubular secretion. J Pharmacol Exp Ther 284: 89
22. Zamboni WC, Stewart CF, Thompson J, Santana VM, Cheshire PJ, Richmond LB, Xiaolong Luo, Poquette C, Houghton JA, Houghton PJ (1998) Relationship between topotecan systemic exposure and tumor response in human neuroblastoma xenografts. J Natl Cancer Inst 90: 505