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ORIGINAL ARTICLE

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Phase-I study of a new schedule based on increasing days of topotecan administration associated with dose individualisation

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Abstract *Background*: The most commonly prescribed schedule of topotecan administration is daily for five days, every 21 days. Both pre-clinical and clinical studies suggest that a more protracted schedule may increase its therapeutic index. The current study was undertaken to determine the maximum tolerated number of days with 30-minute i.v. infusion of topotecan daily at fixed area under the plasma concentration-time curve (AUC) (i.e., 35 μg/Lxh). *Patients and methods*: Topotecan was administered i.v. over 30 min. The planned levels of number of days of administration were: 7, 10, 13, 15 and 17. The dose was individualized according to the patient's individual topotecan clearance observed after the first infusion of each cycle. *Results*: Twenty-three patients were enrolled and received 71 cycles of therapy. The 13-day level was defined as the maximum number of days of administration. The main side effects were thrombocytopenia and anaemia, whereas neutropenia was infrequent. The mean (coefficient of variation) observed AUC was 34.6 (21%), and 33.4 (19%) μg/Lxh, for the last day of cycle 1, and of cycle 2, respectively. Confirmed partial responses were observed in one patient with metastatic desmoplastic tumour and in two patients with small round metastatic endocrine carcinoma. *Conclusion:* The recommended number of topotecan administration is 10 days. Beyond the potential clinical interest of topotecan administered for a 10-day period, this is the first trial showing the feasibility of a phase-I study exploring a number of administrations of daily AUC rather than a total dose in mg/m^2.

Keywords Topotecan · Phase-I · Pharmacokinetics · Drug monitoring

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Introduction

Topotecan ([S]-9-dimethylaminomethyl-10-hydroxycamptothecin) has demonstrated antitumour activity in several tumour types, including ovarian cancer and small-cell lung cancer [1, 2]. Topotecan is a water-soluble semi-synthetic analogue of camptothecin that binds to topoisomerase I-DNA complexes, leading to single-stranded, protein-associated DNA breakage and cellular cytotoxicity. Given such a S-phase specificity, topotecan activity is schedule dependent. The most commonly prescribed schedule is daily five times, every 21 days. Both pre-clinical and clinical studies suggest that a more protracted schedule may increase the therapeutic index of this drug. Hochster et al. [3] have obtained a promising activity, associated with a favourable toxicity profile, of a 21-day infusion every 28 days as treatment of refractory ovarian cancer. In mice using a bearing ovarian carcinoma xenograft model, a shift between the curves of efficacy and toxicity was observed when comparing several schedules of administration of the same total dose: prolonged administration of topotecan resulted in better responses and lower toxicity than a shorter schedule of topotecan administration [4].

The current study was undertaken in order to determine the maximum tolerated number of days of 30-minute i.v. infusion of topotecan daily at fixed area under the plasma concentration time curve (AUC) (i.e., 35 μg/L×h). Indeed, due to a large inter-individual pharmacokinetic variability, numerous studies have reported significant relationships between topotecan AUC and its dose-limiting toxicity (DLT) (i.e., neutropenia) [5, 6]. In this study, the control of daily AUC has been

obtained by performing a dose adjustment based on the observed topotecan clearance (CL) at day 1.

Patients and methods

Patient

Patients' inclusions in this study occurred between May 2001 and August 2003. All patients had histologically confirmed, locally advanced or metastatic carcinoma and unresponsive disease to currently available treatments or for which there was no known effective treatment. Patients were required to have a World Health Organization Performance Status (WHO PS) of two or better, no chemotherapy administered within 4 weeks before inclusion, and to be between 18 and 75 years old. Pre-treatment laboratory eligibility requirements included the following: platelet count≥100,000/μL, neutrophil count≥1,500/μL. All patients included gave written informed consent to participate in the protocol, as approved by the regional ethical committee. Excluded were patients with WHO PS of three or four, blood sampling impossibility, prior therapy with nitrosourea or mitomycin C.

Drug administration

Topotecan (Hycamtin, GlaxoSmithKline, Philadelphia, PA, USA) was administered i.v. over 30 min using an electronic infusion pump. The starting level of number of days of administration was seven. The following planned levels were: 10, 13, 15 and 17 days. Courses had to be repeated every 21 days. The DLT was defined as any of the following treatment-related toxicity occurring during the two first cycles: non-hematological grades 3 and 4 adverse events (excluding alopecia); febrile neutropenia or grades 3 and 4 neutropenia with documented infection; grade 4 neutropenia lasting more than five consecutive days; grade 4 thrombocytopenia or thrombocytopenia requiring transfusion; grade 4 anaemia or anaemia requiring transfusion. In the absence of DLT, escalation of the number of days of therapy was prescribed using cohorts of three patients. In the presence of DLT, the number of days level was expanded to include up to six patients in order to better define the toxicity. The maximum-tolerated number of days was defined as the highest level at which two out of six of the patients experienced DLT. Pre-treatment during the 6-month period preceding the topotecan treatment was previously described as having an impact on the treatment toxicity [7]. At any dose, if any patient previously pre-treated (within the 6-month period) experienced a DLT, the cohort of patients was enlarged and stratified according to pre-treated/non-pre-treated status.

Topotecan dosing and pharmacokinetic analyses

For cycle 1, the daily dose for the first 2 days (Di) was calculated according to the target AUC (i.e., 35 μg/Lxh) and predicted a priori topotecan CLp [8] (i.e., CLp = 5.47×CrCl, where CrCl was Cockcroft-Gault creatinine clearance [9] in L/h): Di (μg) = 35×CLp with CL in L/h. For each patient and each cycle, a pharmacokinetic exploration was performed at day 1 and at the last day of topotecan administration. On day 1, blood samples were taken immediately before the 30-minute infusion as well as 5 min before, and 0.5, 1, 2, 4 and 8 h after the end of infusion. Blood samples (4 mL in heparinized tubes) were collected using an indwelling i.v. cannula placed in the arm that did not receive chemotherapy. After immediate centrifugation at 1,500×*g* for 10 min at 4°C, the plasma was separated and stored (−20°C) until analysis was performed at day 2. Total (i.e., lactone plus carboxylate forms) topotecan plasma concentrations were determined using high-performance liquid chromatographic (HPLC) as previously described [10]. Observed topotecan CL (CL_{obs}) at day 1 was obtained by Bayesian estimation using NONMEM program [11] (Version V, level 1.1) and a database composed of 277 topotecan concentrations versus time from 39 patients according to the previously published method [8]: CL was the post hoc value obtained by adding the concentrations versus time of the patient to the database. The daily dose (Dl) on subsequent days (from day 3 to the last day of topotecan treatment) was calculated according to the equation: Dl (μg) = 35×Cl_{obs}. For the subsequent cycles, the initial dose was the same as for the last days of the previous cycle. Drug monitoring equivalent to that of cycle 1 was performed at day 1 of every cycle for adjustment of the daily dose according to the observed clearance. For every cycle, blood samples were obtained at the last day of the cycle 5 min before, and 4 h after the end of topotecan infusion, in order to quantify the intra-patient (within cycle) pharmacokinetic variability. As for data of day 1, topotecan CL was the post hoc value obtained by combining these specific concentrations versus time to the database. This limiting sampling strategy have been previously validated [8].

Follow-up studies

Complete blood counts were obtained on days 5, 7, 10, 13, 15, 17, 19 and 21, as well as every other day for which the absolute neutrophil count was less than 1,000/μL. The patients should have been recovered of any toxicity observed during the previous cycle before receiving the following cycle. Grade 1 thrombocytopenia was tolerated and anaemia could be actively treated by transfusion.

Tumour measurements were performed for every two courses of treatment. Patients were allowed to continue therapy if no disease progression (as defined by the appearance of new lesions or a 50% or greater increase in the products of the bi-dimensional diameters of any measurable lesion) was observed. For patients receiving more than two cycles, radiologic evaluation of the an-

titumour activity was performed every 6 weeks. A response was deemed partial if 50% or greater reduction was observed in the sum of the products of the bidimensional diameters of all measurable lesions when documented by two measurements separated by at least 6 weeks.

Results

The patients' demographics are reported in Table 1. Twenty-three patients have been included in the study. Out of these 23 patients, 10 (one patient in dose level 1, six in dose level 2 and three in dose level 3) have received previous chemotherapy within 6 months preceding inclusion in the study (Table 2).

Toxicity

No grade 3 or 4 toxicity was observed at the first dose level. At dose level 2, the occurrences of DLT led us to stratify the patients into two groups: pre-treated patients (P) and non-pre-treated patients (NP) within 6 months before entering the study.

At this dose level, one out of five NP patients experienced grade 3 thrombocytopenia requiring transfusion. At the same dose level, in the pre-treated group, two out of six patients experienced DLT: one presented grade 4 thrombocytopenia and anaemia after cycle 1, the other presented grade 4 anaemia requiring transfusion after cycle 2. Since the MTD was not reached, the level 3 was explored. Three out of six NP patients experienced a DLT. One patient experienced grade 3 anaemia requiring transfusion after cycle 2. Another experienced grade 4 thrombocytopenia. The third one experienced grade 4 thrombocytopenia and grade 3 anaemia after the first cycle. In the P group, two out of three patients experienced grade 3 anaemia (requiring transfusion) after the first cycle. This dose level was therefore defined as the MTD. Consequently, the recommended number of administration corresponding to a daily topotecan AUC of 35 μg/Lxh is 10 days for all the patients (P and NP).

No non-hematological toxicity was observed. Grades 3 and 4 neutropenia or thrombocytopenia during the two first cycles were all observed between day 17 and 19. For the patients experiencing grade 3 or 4 neutropenia, none experienced concomitant fever or documented infection. Anaemia was usually observed at day 21 or within the first days of the following cycle.

A total of 71 cycles of chemotherapy were administered during this study. Twenty-one patients received at least a minimum of two cycles of chemotherapy. All the cycles were administered without any delay at day 22. At the recommended level (10 days), a total of 11 patients were treated. Four patients (two NP, two P) who were not progressive, received a total of six cycles each without any sign of cumulative toxicity.

Pharmacokinetics

The mean pharmacokinetic parameters observed during the two first cycles are shown in Table 3. At cycle 1, the daily dose from day 3 (Dl) ranged between 315 and 1,016 μg (218 and 639 μg/m^2) illustrating the three-fold inter-individual variability in CL. Figure 1 represents the individual daily topotocan AUC corresponding to the two first cycles. The mean (coefficient of variation) were 48.6 (34%), 34.6 (21%), 37.9 (23%) and 33.4 (19%) μg Lxh at day 1 of cycle 1, last day of cycle 1, day 1 of cycle 2 and last day of cycle 2, respectively. At day 1 of cycle 1, the mean percentage of difference between targets daily AUC (i.e., 35 μg/Lxh) and observed AUC was +39% leading to a change of the daily dose higher than 20% for 14 patients (dose decrease for all but one). At day 1 of cycle 2, the mean percentage of difference between target daily AUC and observed AUC at day 1 of cycle 1 was +8% leading to a change of the daily dose larger than 20% for seven patients.

Efficacy

Although this phase-I trial was designed to define MTD, some patients presented a response or a clinical benefit

Table 1 Characteristics of the 23 patients

Characteristics	Mean (range)
Age (year)	55 (43–67)
Body surface area[a] (m^2)	1.7 (1.4–2.0)
Body weight (kg)	66 (45–103)
Serum creatinine (μmol/L)	78 (41–122)
Creatinine clearance[b] (mL/min)	84 (37–158)
	Number
Male/Female	9/14
WHO PS: 0/1/2	6/16/1
Previous chemotherapy: Yes/No	19/4
Chemotherapy within the 6-month period preceding inclusion: Yes/No	10/13
Tumour type: ovarian/renal cell carcinoma/endocrine/desmoplastic/uterine/colon/sarcoma/other	4/4/4/1/2/1/2/5

[a]Calculated according to the Dubois formula
[b]Calculated according to the Cockcroft-Gault equation [9]

Table 2 Haematological toxicity: number of cycles 1 or 2 followed by grades 3 and 4 (number of cycles requiring transfusion)

Level: no. of days of administration	No. of patients	No. of cycles	Neutropenia		Thrombocytopenia		Anaemia	
			Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
7 days	3	6	0	0	0	0	0	0
10 days								
Non-pre-treated[a]	5	10	3	1	2 (1)	0	2 (1)	0
Pre-treated*	6	11	1	0	1	1 (1)	0	2 (2)
13 days								
Non-pre-treated	6	11	0	2	0	2 (2)	5 (2)	0
Pre-treated	3	6	0	0	0	0	3 (2)	0

[a]Patient pre-treated (or not) within 6 months preceding inclusion in the study

Table 3 Topotecan clearances: mean values and percentage of change within and between cycles

	Cycle 1			Cycle 2		Cycle 2 versus. Cycle 1
	CL (L/h/m^2)	CL (L/h)	Change within cycle[b]	CL (L/h)	Change within cycle[b]	Change between cycles[c]
N	23	23	23	22	20	22
Mean (±SD[a])	12.5 (±3.1)	21.1 (±5.0)	+1% (±21%)	20.5 (±5.3)	+9% (±19%)	−1% (±23%)
Range	6.2–18.3	9.0–29.0	−64% to +28%	8.9–30.8	−25% to +37%	−36% to +57%

[a]Standard deviation for inter-individual variability
[b]$(CL_{last\ day}–CL_{day\ 1})\times100/CL_{day\ 1}$
[c]$(CL_{day\ 1\ cycle\ 2}–CL_{day\ 1\ cycle\ 1})\times100/CL_{day\ 1\ cycle\ 1}$

during the treatment. In particular, one young man with metastatic desmoplastic small round cell tumour experienced a confirmed partial response. He received six cycles of treatment. The response lasted 6 months thereafter. Two other patients with progressive metastatic endocrine carcinoma, previously refractory to anthracyclin based regimen, experienced minor response. They received six cycles of treatment. Their durations of response were 14 and 24 months, respectively. At last, one patient with bad prognosis renal cell metastatic carcinoma, rapidly progressive under immunotherapy, was stabilized during 6 months with clear clinical benefit. Out of four patients with ovarian carcinoma (only patients with cisplatin-taxans refractory or early relapsing tumours), none experienced radiological or biological (CA-125) response.

Discussion

Two different rationales support the conduct of new phase-I trials for topotecan. First, numerous pre-clinical studies suggest that protracted schedules of administration for topotecan could produce greater antitumour effect than a unique bolus administration [12]. In mice ovarian carcinoma xenograft model, the optimal schedule corresponded to 20 daily injections. The toxicity was maximal when the same total dose was delivered within 5 and 10 days ; 40- and 80-day schedules were associated with lower efficacy [4]. Second, this compound produces a high level of hematological toxicity. Weekly schedule of topotecan is associated with reduced myelosuppression but further studies are needed to confirm that efficacy is maintained [13]. Therefore, we designed a clinical trial aimed at assessing the toxicity pattern of a repeated daily schedule of topotecan administration.

Regarding the large inter-individidual pharmacokinetic variability of topotecan, an AUC-dosing was performed: a target daily AUC was fixed rather than a fixed daily dose in mg or mg/m^2. By using an a posteriori Bayesian adaptation according to the observed clearance at day 1, the mean inter-individual variability in plasma AUC was 20% with mean values close to the target AUC for both cycles. We observed a large inter-individual variability in clearance expressed in L/h/m^2 that retrospectively confirms the benefit of this therapeutic drug monitoring and individualised topotecan dosing. We may suppose that a similar phase I but based on dose calculated in mg/m^2 would be associated with a larger toxicity discrepancy between patients included at the same level of number of days of administration. However, the toxicity results did not confirm the stratification criteria (i.e., chemotherapy during the 6-month period based on previous observations and the first results at level 1) since the maximum tolerated level was the same in both sub-populations. Although pre-treatment do have an impact on topotecan toxicity, the criteria is probably not sufficiently accurate to describe the bone marrow reserve of the patients that is likely also dependent on the number of lines and the type of prior therapy.

The relationship between predicted topotecan CL and CrCl used for calculation of the initial dose of topotecan (i.e., CLp = 5.47×CrCl [8]), overestimated the topotecan CL leading to a dose reduction for 19/23 patients. More recently, we have updated this relationship by analysing a larger pharmacokinetic data set ($n = 190$ patients): CLp = (12.8 + 2.1×CrCl)×(1–0.12×PS), with CrCl in L/h, and PS for WHO PS [14]. By using this relationship for the initial dosing, the mean AUC (range) and corresponding coefficient of variation would have been 37.1 (23.2–59.9) µg/L×h and 25%. These values are similar to those obtained thanks to the drug monitoring. Then, we recommend this relationship for prediction of topotecan CL for future studies.

Intra-individual pharmacokinetic variability within and between cycles were limited (Table 3) leading to a good adequacy for most of the patients between target and observed AUC (Fig. 1) since the last day of cycle 1.

The value of 35 µg/L×h for the daily AUC may be considered partly as empirical. This value was chosen as the third of the recommended daily AUC corresponding to the 5-day schedule for patients who did not receive any chemotherapy during the 6-month period preceding topotecan [7]. The overall AUC corresponding to the recommended number of days of treatment (i.e., 10×35 = 350 µg/L×h) was lower than that of the 5-day schedule in these patients (525 µg/L×h) indicating that fractionation of topotecan doses does not allow to increase the total AUC which may be tolerated. Contrary to Hoskins et al who observed the same DLT (i.e., neutropenia) when they compared 1.75 mg/m^2 once a week and 1.5 mg/m^2 for 5 days repeated every 21days [15] (but, the two regimen were not equitoxic), the DLT associated with the 13-day schedule of administration is not the same as that of the 5-day schedule: anaemia was the DLT, whereas neutropenia is the DLT of the regular schedule. It has been shown that topotecan decreases the hypoxia-inducible factor 1 α (HIF-1 α) protein accumulation [16]. Moreover, the mechanism by which topotecan exerts its HIF-1 α inhibition is distinct from the one leading to cytotoxicity effect. We may hypothesize that the levels of topotecan concentrations corresponding to the 13-day schedule are more favourable to the first effect, and then responsible for these anaemia. We also do not know if this mechanism is involved in the tumour shrinkage we observed in one patient with rapidly progressive sporadic cell carcinoma and in two patients with endocrine tumours. The literature suggest that oncogenesis of that type of tumour could be linked to mutations in VHL gene and, consequently, in HIF dysfunction [17, 18].

Nevertheless, we believe that our results suggest a phase-II trial at the recommended dose in patient with endocrine tumours including pheochromocytomas. In case of favourable results of phase-II trials, the perspective to develop this schedule and particularly to use it as a standard treatment require to benefit from a more convenient way of administration. Oral topotecan is actually under development [19]. This formulation would be attractive for such a schedule. A limiting sampling strategy has been also developed and validated for oral administration [14]. However, it is associated with a larger inter- and intra-individual pharmacokinetic variability that may compromise the daily targeted value of topotecan AUC [14]. Therefore, programmable pump for IV administration remains so far the only way to combine outcome administration and reproducible AUC.

In conclusion, beyond the potential clinical interest of topotecan administered for 10-day period, this is the first trial showing the feasibility of a phase-I study exploring a number of administration of daily AUC rather than a total dose in mg/m^2.

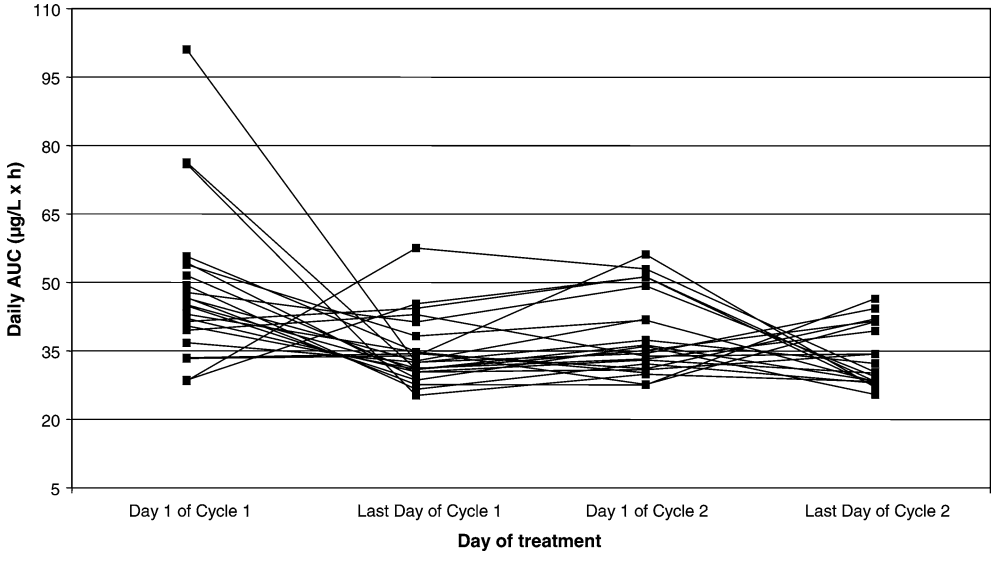

Fig. 1 Observed area under the curve of the topotecan plasma concentrations versus time (*AUC*)

References

1. Brogden RN, Wiseman LR (1998) Topotecan. A review of its potential in advanced ovarian cancer. Drugs 56:709–723
2. Ormrod D, Spencer CM (1999) Topotecan: a review of its efficacy in small cell lung cancer. Drugs 58:533–551
3. Hochster H, Wadler S, Runowicz C, Liebes L, Cohen H, Wallach R, Sorich J, Taubes B, Speyer J (1999) Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy. New York Gynecologic Oncology Group. J Clin Oncol 17:2553–2561
4. Guichard S, Montazeri A, Chatelut E, Hennebelle I, Bugat R, Canal P (2001) Schedule-dependent activity of topotecan in OVCAR-3 ovarian carcinoma xenograft: pharmacokinetic and pharmacodynamic evaluation. Clin Cancer Res 7:3222–3228
5. O'Reilly S, Rowinsky EK, Slichenmyer 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 14:3062–3073
6. Dennis MJ, Beijnen JH, Grochow LB, van Warmerdam LJ (1997) An overview of the clinical pharmacology of topotecan. Semin Oncol 24:S5
7. Montazeri A, Culine S, Laguerre B, Pinguet F, Lokiec F, Albin N, Goupil A, Deporte-Fety R, Bugat R, Canal P, Chatelut E (2002) Individual adaptive dosing of topotecan in ovarian cancer. Clin Cancer Res 8:394–399
8. Montazeri A, Boucaud M, Lokiec F, Pinguet F, Culine S, Deporte-Fety R, Albin N, Laguerre B, Goupil A, Bugat R, Canal P, Chatelut E (2000) Population pharmacokinetics of topotecan: intraindividual variability in total drug. Cancer Chemother Pharmacol 46:375–381
9. Cockcroft-Gault DW, Gault MH (1976) rediction of creatinine clearance from serum creatinine. Nephron 16:31–41
10. Rosing H, Doyle E, Davies BE, Beijnen JH (1995) High-performance liquid chromatographic determination of the novel antitumour drug topotecan and topotecan as the total of the lactone plus carboxylate forms, in human plasma. J Chromatogr B Biomed App 668:107–115
11. Beal SL, Sheiner LB (1982) Estimating population kinetics. Crit Rev Biomed Eng 8:195–222
12. Gerrits CJ, de Jonge MJ, Schellens JH, Stoter G, Verweij J (1997) Topoisomerase I inhibitors: the relevance of prolonged exposure for present clinical development. Br J Cancer 76:952–962
13. Treat J (2003) Weekly topotecan in the management of lung cancer. Lung Cancer 41(Suppl 4):S27–S31
14. Léger F, Loos WJ, Fourcade J, Bugat R, Goffinet M, Mathijssen RH, Verweij J, Sparreboom A, Chatelut E (2004) Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. Br J Cancer 90:343–347
15. Hoskins P, Eisenhauer E, Eare S, Roy M, Drouin P, Tuart G, Bryson P, Grinshaw R, Capstick V, Zee B (1998) Randomized phase II study of two schedules of topotecan in previosly treated patients with ovarian cancer: a national cancer institute of Canada clinical trials group study. J Clin Oncol 16:2233–2237
16. Rapisarda A, Uranchimeg B, Sordet O, Pommier Y, Shoemaker RH, Melillo G (2004) Topoisomerase I-mediated inhibition of hypoxia-inducible factor 1: mechanism and therapeutic implications. Cancer Res 64:1475–1482
17. Kim WY, Kaelin WG (2004) Role of VHL gene mutation in human cancer. J Clin Oncol 22:4991–5004
18. Couvelard A, O'Toole D, Turley H, Leek R, Sauvanet A, Degott C, Ruszniewski P, Belghiti J, Harris AL, Gatter K, Pezzella F (2005) Microvascular density and hypoxia-inducible factor pathway in pancreatic endocrine tumours: negative correlation of microvascular density and VEGF expression with tumour progression. Br J Cancer 92:94–101
19. Schellens JH, Creemers GJ, Beijnen JH, Rosing H, Boer-Dennert M, McDonald M, Davies B, Verweij J (1996) Bioavailability and pharmacokinetics of oral topotecan: a new topoisomerase I inhibitor. Br J Cancer 73:1268–1271