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ORIGINAL ARTICLE

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Modulation of irinotecan with cyclosporine: a phase II trial in advanced colorectal cancer

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Abstract *Introduction*: Despite the extensive clinical experience with irinotecan, significant concerns remain regarding its toxicity. In a phase I trial, we modulated irinotecan pharmacokinetics by inhibiting biliary excretion of SN-38, the active metabolite of irinotecan, using cyclosporine. The modulation appeared to decrease the gastrointestinal toxicity of irinotecan and suggested that irinotecan activity might also be retained. Hence, we conducted this phase II trial in patients with colorectal cancer (CRC) to further evaluate the toxicity and activity of irinotecan modulated with cyclosporine. *Patients and Methods*: Sixteen patients with 5-fluorouracil refractory CRC were treated. Cyclosporine (5 mg/kg) was administered as a 6-h infusion and irinotecan (60 mg/m^2/day, 90-min infusion) was started 3 h after initiation of the Cyclosporine. Both agents were given weekly for 4 weeks, every 6 weeks. Responses were assessed every 12 weeks, and toxicity was monitored weekly. *Results*: Sixteen patients were evaluable for toxicity and 11 for response. There was 1 partial response (6%). Five patients had SD lasting a median of 12 weeks. Grade 3/4 diarrhea was observed in only 13% of the patients. *Conclusion*: Pharmacokinetic modulation of irinotecan using parenteral cyclosporine appears to decrease the incidence of diarrhea in CRC patients. Given the modest activity of irinotecan monotherapy, a larger study would be required to assess if the modulation improves the toxicity without compromising this activity. The available clinical data suggest that pharmacokinetic modulation of irinotecan should be evaluated further to define its optimal clinical utility.

Keywords Irinotecan · Cyclosporine · Pharmacokinetic modulation · Colorectal cancer

Two of the co-authors: Edem Agamah (owns shares of Pfizer) and Mark J. Ratain [Co-inventor on several patents (pending/issued) related to the modulation or irinotecan and/or its Pharmacogenetics] would like to declare their potential conflicts of interest.

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Introduction

5-fluorouracil (5-FU) based regimens have been the mainstay of therapy for advanced CRC for almost five decades, with single-agent response rates of about 15-20% [1]. The recent addition of irinotecan and oxaliplatin to 5-FU based regimens has resulted in higher response rates and improved survival [2, 3]. However, such treatment regimens often are associated with severe toxicity [3–8]. Both the efficacy and tolerability of the available CRC regimens still need to be optimized.

Irinotecan (monotherapy) was first approved in the United States in1996, and was the standard of care for second line therapy in 5-FU-refractory CRC at the inception of the current trial [4, 5]. Diarrhea and myelosuppression have been the most clinically significant toxicities of irinotecan, with diarrhea being more common. Irinotecan-mediated acute diarrhea occurs due to inhibition of cholinesterase activity resulting in a cholinergic syndrome. Delayed diarrhea arises as a consequence of direct enteric injury from SN-38, the active metabolite of irinotecan [9, 10]. The incidence of delayed diarrhea is also dependent on the

irinotecan administration schedule; about 35% of patients treated with weekly irinotecan experience grade 3 or 4 diarrhea compared to only 19% of patients treated on the once every 3 week schedule [8]. Thus, there is a significant amount of concern regarding the gastrointestinal toxicity of irinotecan [11, 12].

Irinotecan has complex pharmacology involving multiple activation and inactivation pathways as well as hepatobiliary transport. It is a prodrug, which is converted to its active metabolite SN-38 by carboxylesterases [13]. Only a small fraction of the administered irinotecan is converted to SN-38, and the remaining parent drug is metabolized by cytochrome P450 3A (CYP3A) or excreted via hepatic or renal transport [9, 14]. SN-38 is detoxified by the polymorphic enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) to SN-38 glucuronide (SN-38G) [15, 16]. The importance of biliary excretion of SN-38 is well established [9, 10], and a previous study demonstrated that a ''biliary index'' (an indirect measure of SN-38 biliary excretion) correlates with the risk of diarrhea on the weekly schedule of irinotecan [17]. Thus, pharmacokinetic modulation strategies to reduce SN-38 excretion into the bile have been pursued with agents that either inhibited biliary excretion of SN-38 or induced SN-38 glucuronidation (thus, decreasing the SN-38 available for biliary elimination), with the hypothesis that such modulation would improve the therapeutic index by decreasing the gastrointestinal toxicity of irinotecan [18–21]. Initial experiments in rodents demonstrated that irinotecan modulation with cyclosporine A decreased both renal and non-renal clearance of irinotecan, and led to a significant increase in the area under the time curve (AUC) of irinotecan, SN-38, and SN-38G, respectively [18]. Modulation with phenobarbital an inducer of glucuronidation was demonstrated to significantly increase SN-38 glucuronidation [19].

Based on these non-clinical findings, Ratain and colleagues performed a phase I study to evaluate the modulation of irinotecan pharmacokinetics; first with cyclosporine alone and then by adding phenobarbital [21]. Patients with refractory malignancies were treated with a 6-h cyclosporine infusion followed by escalating doses of irinotecan (dose levels 25, 40, 50 and 60 mg/m^2) given over 90 min and administered 3 h into the cyclosporine infusion, and further irinotecan dose escalation was performed by adding phenobarbital to irinotecan and cyclosporine. At the inception of the current trial, the preliminary data analysis of the phase I trial demonstrated 2 partial responses amongst 18 evaluable patients, and both responding patients had metastatic CRC. Dose limiting diarrhea was observed in only 1 patient at an irinotecan dose of 60 mg/m^2 in combination with cyclosporine. Compared to historical data of patients treated with irinotecan administered at similar doses on the weekly schedule; cyclosporine and irinotecan co-administration increased SN-38 exposure, reduced the clearance, and increased the half-life of irinotecan, SN-38 and SN-38G [21]. The clinical data suggested that the diarrhea could be diminished, and the activity might also be maintained. Hence, we initiated this phase II study of irinotecan and cyclosporine to better characterize the toxicity and activity of the combination in patients with 5-FU refractory CRC.

Patients and methods

Patient eligibility

Patients with histologically confirmed metastatic or locally recurrent adenocarcinoma of the colon or rectum who had failed previous 5-FU therapy were eligible to participate in this study. 5-FU-refractory disease was defined as either progression of disease within 6 months of adjuvant 5-FU chemotherapy, or disease progression during or following completion of one 5-FU-based chemotherapy regimen for metastatic disease. Additional eligibility criteria included bidimensionally measurable disease; age ≥18 years; ECOG or Zubrod performance status of 0-2; life expectancy ≥12 weeks; and adequate organ function defined as: white blood cell count ≥3,500/μl; absolute neutrophil count ≥1,500/μl; platelet count ≥100,000/μl; total bilirubin ≤ 1.5 mg/dl; serum transaminases ≤ 3 × upper limit of normal, serum creatinine ≤ 1.5 mg/dl *or* calculated creatinine clearance ≥ 60 ml/min. Patients were required to have no radiation to sites of measurable disease; no anticancer therapy for at least 4 weeks before study entry; no history of second malignancy within 5 years other than non-melanoma skin cancers; no uncontrolled pre-existing medical conditions; use of acceptable form of birth control (pregnant or lactating patients were excluded); no central nervous system metastases requiring concomitant steroids or anticonvulsants. All patients participating in the trial provided written informed consent before study enrollment in accordance with institutional and federal guidelines.

Pretreatment and follow-up studies

At study entry, all patients underwent a complete history and physical examination. Assessment of measurable disease by imaging studies (CT or MRI scans) was performed within 4 weeks of study entry. All patients were required to undergo a complete history and physical examination prior to start of each treatment cycle. Hematologic parameters were followed weekly and complete serum chemistries were assessed every 2 weeks while on therapy. Tumor response evaluations were performed after the first two cycles of therapy and every two cycles thereafter. A research nurse contacted patients weekly by phone or in person for a toxicity assessment, and completed a toxicity form each week.

Study design

This was a multi-institutional study conducted at nine sites through the University of Chicago Phase II Consortium. Cyclosporine was administered at a dose of 5 mg/kg, as a 6-h infusion on a weekly schedule for 4 weeks followed by a 2-week rest period. Irinotecan (60 mg/m^2/day, 90 min infusion) administration was started 3 h after initiation of the Cyclosporine. Therapy was continued for at least two cycles unless the patient met withdrawal criteria or had progressive disease. NCI common toxicity criteria (CTC) version 2.0 was used to grade the toxicity.

Response and toxicity criteria

Two-dimensional measurement criteria were used to classify response using World Health Organization response criteria as defined below. Patients with partial response (PR) and complete response (CR) or stable disease (SD) were allowed to continue therapy if they did not experience severe toxicity. CR was defined as complete disappearance of all clinically detectable disease for at least 4 weeks. PR was defined as ≥50% decrease from baseline in the sum of the products of two perpendicular diameters of all measured lesions for at least 4 weeks without appearance of any new malignant disease. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions over the smallest sum observed; reappearance of any lesion that had disappeared; appearance of any new lesions. Stable disease was designated for all patients that did not qualify for CR, PR or PD.

Statistical considerations

The primary objective of the trial was to determine whether the proposed modulation strategy could reduce the incidence of grade 3-4 diarrhea observed with irinotecan monotherapy. A three-stage design was utilized to test the null hypothesis that the underlying rate of grade 3-4 diarrhea was 0.25 against the alternative that it was 0.10. Patients were to be accrued in three stages of 15 patients each, for a maximum sample size of 45. The trial was to be terminated early if more than 4/15 or more than 6/30 patients experienced grade 3-4 diarrhea. The null hypothesis was to be rejected if fewer than 8/45 patients experienced grade 3-4 diarrhea. This study design had a Type I error rate of 0.09 and a Type II error rate of 0.08. The probabilities of stopping after the first and second stages if the true rate was 0.25 (i.e., if the null hypothesis were true) were 0.31 and 0.67, respectively. Since it was possible that the true rate of grade 3-4 diarrhea could be less than 0.10, a binomial distribution was to be utilized to construct a 90 upper confidence bound. Hence, if the true rate of diarrhea were only 0.05, then this upper bound would be 0.14 or less with probability of 0.81. The response rate for this regimen was not expected to be much different than that observed in previous Phase II trials of irinotecan as reported at the time of the study (~15%). An early stopping rule was put in place such that further accrual would be terminated if fewer than 1/15 or fewer than 2/30 responses were observed in the first two stages of the trial (since such low response rate would be unlikely if the true response rate was 0.15).

Overall survival and progression free survival was estimated for all enrolled patients using the Kaplan-Meier methods. Confidence intervals for the median survival times were obtained as described in Brookmeyer and Crowley [22].

Results

Sixteen patients were enrolled on the study between August 1999 and April 2001. All patients were evaluable for toxicity, and 11 patients were evaluable for response. The study was terminated earlier than planned due to very slow accrual after Saltz and colleagues reported their promising data using irinotecan in combination with 5-FU and leucovorin for metastatic CRC [3]. The median age of the patients on study was 62 years (range 42–85). All patients had previously received chemotherapy; 13 patients failed primary adjuvant therapy and three subjects progressed on 5-FU administered for metastatic disease. Other patient characteristics are summarized further in Table 1.

Response to treatment

Response data are summarized in Table 2. Five patients did not complete the first two cycles of therapy: one

Table 1 Patient Characteristics

Characteristics	No. of patients (%)
Patients enrolled	
Men	8 (50%)
Women	8 (50%)
Median age (years)	62
Range (years)	42-85
ECOG performance status	
0	8 (50%)
1	8 (50%)
Primary tumor site	
Colon	13 (81%)
Rectum	3 (19%)
Prior radiation therapy	
Yes	2 (12%)
No	14 (88%)
Prior adjuvant therapy	
Yes	14 (88%)
No	2 (12%)
Number of prior chemotherapies	
1	13 (81%)
2	3 (19%)

Table 2 Best response to therapy

Best response	Patients ($n = 16$)	
	Number	(%)
Complete response	0	(0)
Partial response	1	(6)
Stable disease	5	(32)
Progressive disease	6	(37)
Not evaluable	4	(25)

patient did not receive any irinotecan therapy due to cyclosporine toxicity experienced after the first dose of cyclosporine and was not evaluable for response; four patients did not complete the first two cycles of therapy; three due to adverse events [one patient required prolonged treatment of a psoas abcess (non-neutropenic) that was diagnosed during the first cycle of therapy; 1 patient experienced grade 3 diarrhea during cycle 1 and withdrew consent; one patient did not wish to continue with cyclosporine (patient attributed the gastrointestinal toxicities to cyclosporine) and had to be taken off study] and one due to disease progression. All 16 patients were included in the intent-to-treat analysis for response assessment. There were no CRs, and one PR (12 week duration), for a response rate of 6.3% (90% CI:. 3%, 26.4%). Five patients experienced disease stabilization for a median of 12 weeks (range 12–24 weeks). The median progression free survival was 14.7 weeks (95% CI: 10.0-24.4) and median overall survival was 43.7 weeks (95% CI: 17.4-78.9).

Adverse events

The toxicity data are summarized in Table 3. One patient experienced a grade 3 hypersensitivity reaction during the first cyclosporine infusion, and was taken off the study prior to receiving any irinotecan. Hence, 16 patients were evaluable for cyclosporine toxicity, and 15 patients were evaluable for toxicity for both study agents.

Gastrointestinal toxicity consisted mainly of mild (grades 1–2) nausea/emesis and diarrhea. Only 2 patients experienced grade 3 diarrhea, and no treatment related grade 4 gastrointestinal toxicity was observed. The grade 3-4 diarrhea rate was 12.5% (90% CI: 2.3%-34.4%). Hematologic toxicity, though common, was mild, with only single episodes of grade 3 neutropenia and anemia. Two patients with grade 3 renal dysfunction had obstructive uropathy. Two episodes of grade 3 infections occurred in non-neutropenic hosts.

Discussion

The initial enthusiasm associated with FDA approval of irinotecan for the treatment of CRC was balanced against concerns about the toxicity observed during the early clinical development of the drug. In general, as experience with the irinotecan increased, clinicians learned to manage the toxicities better with aggressive supportive care. However, the fatal adverse events observed in large cooperative group trials re-intensified the concerns regarding irinotecan-mediated toxicities [13, 14]. Thus, strategies to improve the therapeutic index of

Table 3 Adverse events ($n = 16$)

Adverse event	Grade 1 No. (%)	Grade 2	Grade 3	Grade 4
Constitutional				
Fatigue	2 (13%)	3 (20%)		
Anorexia	1 (7%)	1 (7%)		
Fever	1 (7%)			
Gastrointestinal				
Nausea/emesis	1 (7%)	1 (7%)		
Diarrhea	2 (13%)	2 (13%)	2 (13%)	
Bowel obstruction				2 (13%)
Hematological				
Anemia	7 (47%)	4 (27%)	1 (7%)	
Leukopenia	3 (20%)	2 (13%)	1 (7%)	
Neutropenia	3 (20%)	3 (20%)	1 (7%)	
Febrile neutropenia	0	0	0	0
Chemistry				
SGOT	5 (33%)			
SGPT	3 (20%)			
Bilirubin	1 (7%)			
Creatinine		1 (7%)	2 (13%)	
Miscellaneous				
Infection		1 (7%)	2 (13%)	
Hypersensitivity			1[a]	

[a]One patient experienced a hypersensitivity reaction to cyclosporine. The toxicity is listed in the table; however, the other reported adverse events are based on data obtained from the remaining 15 patients who received both study agents

irinotecan could be quite useful in clinical practice. This is the first report of a phase II trial utilizing pharmacokinetic modulation of irinotecan designed to improve the therapeutic index of irinotecan.

In this trial, we sought to decrease the gastrointestinal toxicity of irinotecan without compromising its activity based on our preliminary phase I experience with cyclosporine modulation [21]. The 13% rate of grade 3 diarrhea we observed was lower than reported with standard dose of irinotecan administered on a weekly schedule [8]. One partial response was observed, suggesting that the activity of irinotecan was retained with cyclosporine modulation. However, broadening indications for the use of irinotecan in CRC [3] during the conduct of the study significantly hindered our accrual and led us to terminate the study earlier than planned. The small sample size limits the power to make any significant conclusions regarding the clinical response or toxicity of the regimen. However, one potential reason for the observed rates of both activity and toxicity on the trial might be that the irinotecan dose utilized was too low. Our prior phase I data with this modulation strategy (21, 23) would refute this notion; however, the lack of pharmacokinetic data in the current trial prevents us from providing direct evidence for or against such a possibility. In retrospect, the ideal trial design to address the issue might have been to incorporate pharmacokinetic sampling as part of the trial.

In our previous phase I study [21]; objective responses were observed without significant change in the toxicity profile even after the addition of phenobarbital to cyclosporine and irinotecan. The low SN-38 AUC observed in the phase I study amongst the responders suggests that intratumoral levels of SN-38 might be more important than systemic SN-38 exposure. Hence, pursuing strategies that can decrease the gastrointestinal toxicity of SN-38 by reducing SN-38 systemic exposure and allow for higher circulating levels of irinotecan available for intratumoral conversion to SN-38 might be the more optimal modulation strategy. Analysis of the data after completion of the phenobarbital containing arm of our phase I trial suggests that such a goal might be better achieved utilizing the CSA-phenobarbital combination for modulating irinotecan pharmacokinetics [23].

Chester and colleagues have recently reported results from a larger phase I study using oral cyclosporine for irinotecan pharmacokinetic modulation [24], and their data also suggest that irinotecan activity can be maintained while reducing its toxicity. Given the differences in the study design it is not appropriate to make direct comparisons of the data from the two trials. However, the changes in irinotecan clearance and SN-38 exposure in the Chester trial were of similar magnitude to those observed in our phase I trial. Furthermore, the pharmacokinetic data in the trial conducted by Chester and colleagues were comparable to historical data of irinotecan administered at the MTD on the same schedule [24]. Thus, oral cyclosporine provides a potentially more convenient approach for application of the modulation strategy.

Several other approaches to improve the therapeutic index of irinotecan also appear promising. Intestinal bacteria-derived β-glucuronidase can convert the nontoxic SN-38G to SN-38, thus causing direct gastrointestinal mucosal injury and toxicity, and inhibition of bowel β-glucuronidase using neomycin has also been demonstrated to decrease diarrhea in a small clinical trial [25]. Govindrajan et al. [26] have reported a significant decrease in the gastrointestinal toxicity of irinotecan when co-administered with thalidomide without any compromise in the activity of the regimen. Since there were no pharmacokinetic data collected by Govindrajan and colleagues, we have recently initiated a trial to investigate the potential role of pharmacokinetic interaction between thalidomide and irinotecan to explain the reported clinical observations.

Despite the progress made thus far with various strategies, much remains to be accomplished to improve the therapeutic index of irinotecan. The existing clinical data [23, 24] support the hypothesis that led to development of this modulation strategy, and suggest that the approach needs to be validated further in larger randomized prospective studies. Ideally, incorporating the pharmacokinetic modulation with other strategies that complement it should also be pursued. A recently concluded pharmacogenetic study of irinotecan [27] provides evidence that individuals with a genetic defect in the *UGT1A1* gene are at an increased risk of severe irinotecan toxicity, and these subjects may stand to gain the most by application of modulation strategies. Hence, they might perhaps be the most appropriate patient population for further development of this concept.

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References

1. Vokes EE, Golomb HM (2003) (eds) Oncologic therapies, 2nd edn. In: Kindler HL, Schilsky RL, Colorectal cancer. Springer, Berlin Heidelberg New York, pp 425–438
2. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
3. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905–914
4. Rougier P, Bugat R, Douillard JY, Culine S, Suc E, Brunet P, Becouarn Y, Ychou M, Marty M, Extra JM, Bonneterre J, Adenis A, Seitz JF, Ganem G, Namer M, Conroy T, Negrier S, Merrouche Y, Burki F, Mousseau M, Herait P,

Mahjoubi M (1997) Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naïve patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 15:251–260
5. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P (1998) Randomized trial of irinotecan plus supportive care versus supportive care alone after flurouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418
6. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C (1998) Randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412
7. Vanhoefer U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM (2001) Irinotecan in the treatment of colorectal cancer: clinical overview. J Clin Oncol 19:1501–1518
8. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht R (2003) Phase III comparision of two irinotican dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 21:807–814
9. Slatter JG, Schaaf LJ, Sams JP, Feenstra KL, Johnson MG, Bombardt PA, Cathcart KS, Verburg MT, Pearson LK, Compton LD, Miller LL, Baker DS, Pesheck CV, Lord RS 3rd (2000) Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following I.V. infusion of [(14)C]CPT-11 in cancer patients. Drug Metab Dispos 28:423–433
10. Araki E, Ishikawa M, Iigo M, Koide T, Itabashi M, Hoshi A (1993) Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. Jpn J Cancer Res 84:697–702
11. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: Summary finding of an independent panel. J Clin Oncol 19:3801–3807
12. Sargent DJ, Niedzwiecki D, O'Connell MJ, Schilsky RL (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. N Engl J Med 345:144–145
13. Humerickhouse R, Lohrbach K, Li L, Bosron WF, Dolan ME (2000) Characterization of CPT-11 hydrolysis by human liver carboxylesterase isoforms hCE-1 and hCE-2. Cancer Res 60:1189–1192
14. Santos A, Zanetta S, Cresteil T, Deroussent A, Pein F, Raymond E, Vernillet L, Risse ML, Boige V, Gouyette A, Vassal G (2000) Metabolism of irinotecan (CPT-11) by CYP3A4 and CYP3A5 in humans. Clin Cancer Res 6:2012–2020
15. Iyer L, King CD, Whitington PF, Green MD, Roy SK, Tephly TR, Coffman BL, Ratain MJ (1998)Genetic predisposition to the metabolism of irinotecan (CPT-11): Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 101:847–854
16. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ (1994) Metabolic fate of irinotecan in humans: Correlation of glucuronidation with diarrhea. Cancer Res 54:3723–3725
17. Gupta E, Mick R, Ramirez J, Wang X, Lestingi TM, Vokes EE, Ratain MJ (1997) Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. J Clin Oncol 15:1439–1443
18. Gupta E, Safa AR, Wang X, and Ratain MJ (1996) Phamacokinetic modulation of irinotecan and metabolites by cyclosporin A. Cancer Res 56:1309–1314
19. Gupta E, Wang X, Ramirez J and Ratain MJ (1997) Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and Phenobarbital. Cancer Chemother Pharmacol 39:440–444
20. Ratain MJ, Gupta E (inventors). Camptothecin drug combinations and methods with reduced side-effects. United States patent no. 5,786,344, 28 July 1998
21. Ratain MJ, Goh BC, Iyer L et al (1999) A Phase I study of irinotecan with pharmacokinetic modulation by cyclosporine A and phenobarbital. Proc Am Soc Clin Oncol 18:202a
22. Brookmeyer R and Crowley JJ (1982) A confidence interval for the median survival time. Biometrics 38:29–41
23. Innocenti F, Undevia SD, Ramírez J, Mani S, Schilsky RL, Vogelzang NJ, Prado M, Ratain MJ (2004) A phase I trial of pharmacological modulation of irinotecan with cyclosporine A and Phenobarbital. Clin Pharm Ther 76:490–502
24. Chester JD, Joel SP, Cheeseman SL, Hall GD, Braun MS, Perry J, Davis T, Button CJ, Seymour MT (2003) Phase I and pharmacokinetic study of intravenous irinotecan plus oral ciclosporin in patients with fluorouracil refractory metastatic colon cancer. J Clin Oncol 21:1125–1132
25. Kehrer DF, Sparreboom A, Verweij J, de Bruijn P, Nierop CA, van de Schraaf J, Ruijgrok EJ, de Jonge MJ (2001) Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. Clin Cancer Res 7:1136–1141
26. Govindrajan R (2000) Irinotecan and thalidomide in metastatic colorectal cancer. Oncology 16:29–32
27. Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ (2004) UGT1A1*28 polymorphism is a predictor of neutropenia in irinotecan chemotherapy. J Clin Oncol 22:1382–1388