

Irinotecan Treatment for Recurrent Malignant Glioma Using an Every-3-Week Regimen

Timothy F. Cloughesy, M.D., Emese Filka, M.D., Gillian Nelson, M.D.,
Fairooz Kabbinavar, M.D., Henry Friedman, M.D.,
Langdon L. Miller, M.D., and Gary L. Elfring, M.S.

This phase II study was designed to evaluate the safety, tolerability, and efficacy of irinotecan (CPT-11) in the treatment of adults with malignant glioma. Patients with progressive or recurrent malignant gliomas were enrolled. CPT-11 was administered as a 90-minute intravenous infusion at a dose of 300 mg/m² once a week every 3 weeks. After 2 treatments, doses were increased to 350 mg/m² in those patients without grade III/IV toxicities. Dose modifications were made for toxicities. All 14 patients who enrolled (11 males and 3 females) were treated with CPT-11 and were assessable for survival, response, and toxicity. The majority of patients (86%) had prior surgery. Two patients had a confirmed partial response and 2 patients (14%) had stable disease. Median survival was 24 weeks. Median time to tumor progression was 6 weeks. The primary hematologic toxicity was grade III/IV neutropenia, which was observed in 14% of patients. Infrequent grade III/IV nonhematologic toxicity was observed, possibly because of the concomitant use of anticonvulsants, which may have altered pharmacokinetics. These results suggest that CPT-11 has activity against recurrent malignant glioma using a dosing regimen of 300 mg/m² every 3 weeks showing limited toxicity. The concurrent use of anticonvulsant medications may have played a role in altering pharmacokinetics and thus the maximum tolerated dose in this patient population.

Key Words: CPT-11—Malignant glioma—Irinotecan.

Malignant gliomas are treated with multimodal therapy, including surgery, radiation therapy, and chemotherapy. Treatment with surgery and radiation therapy is seldom curative and only serves to prolong life. These tumors tend to be more resistant to chemotherapy but sometimes respond to chemotherapies (i.e., carmustine, carboplatin, procarbazine, temozolomide, lomustine, and other nitrosoureas).¹ Patients with malignant glioma usu-

ally receive supportive care that includes the use of anticonvulsants to prevent epileptic seizures and corticosteroids such as dexamethasone to help control cerebral edema.^{2,3}

Patients with glioblastoma multiforme (GBM) have a median survival of approximately 10 months, whereas patients with anaplastic astrocytoma have a median survival of approximately 2 to 3 years.¹ Favorable prognostic variables include young age (<40 years), pathology of anaplastic astrocytoma, no more than two prior chemotherapies or surgeries, and Karnofsky Performance Status more than 80%.⁴

Despite progress being made using novel combination therapies of surgery, radiation, and/or chemotherapy, the treatment of recurrent or progressive malignant gliomas remains problematic because of treatment limitations and a typical median time to tumor progression of 8 weeks.

Irinotecan (CPT-11, Camptosar; Pharmacia & Upjohn, Kalamazoo, MI, U.S.A.) is a semisynthetic derivative of camptothecin, an alkaloid obtained from plants such as the *Camptotheca acuminata* tree. It possesses greater aqueous solubility, and greater in vivo and in vitro activity, and is associated with less severe and more predictable toxicity than camptothecin.⁵⁻⁷ CPT-11 is converted by carboxylesterases to its more active lipophilic metabolite, SN-38.⁸ Both camptothecin and SN-38 are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription. In vitro, SN-38 is 250 to 1,000 times more potent than CPT-11 as an inhibitor of topoisomerase I activity.⁹

The area under the plasma concentration versus time curve (AUC) for SN-38 is 2% to 8% of CPT-11.¹⁰ The mean terminal half-life of SN-38 in plasma is longer than that of CPT-11: 11.5 ± 3.8 hours versus 6.3 ± 2.2 hours for the lactone forms.¹¹

The bioactivation of CPT-11 to SN-38 is believed to take place in the liver. SN-38 is further conjugated to a glucuronide (SN-38G). A new metabolite, amino pentane carboxylic acid, has been isolated from human plasma, but neither the SN-38G or amino pentane car-

From the UCLA School of Medicine, Henry Singleton Brain Cancer Research Program (T.F.C., E.F., G.N., F.K.), Los Angeles, California; Duke University Medical Center (H.F.), Durham, North Carolina; and Pharmacia & Upjohn (L.L.M., G.L.E.), Kalamazoo, Michigan, U.S.A.

Supported by a grant-in-aid from Pharmacia & Upjohn, Kalamazoo, Michigan.

Address correspondence and reprint requests to Dr. Timothy F. Cloughesy, UCLA School of Medicine, Department of Neurology, 710 Westwood Plaza, Room 1-230, Los Angeles, CA 90095, U.S.A.

boxylic acid are believed to contribute substantially to the activity or toxicity of CPT-11.¹²

In laboratory studies, CPT-11 has shown activity against tumor xenografts derived from ependymomas, high-grade gliomas, and medulloblastomas.¹³ CPT-11 has been shown to have activity in the treatment of recurrent malignant glioma using a dose of 125 mg/m² weekly for 4 weeks followed by a 2-week rest.^{14,15} It was thought that an every-3-week dosing schedule might be tolerated better by patients and possibly may prove more beneficial.

The primary objective of our study was to determine the efficacy and safety of CPT-11 at a starting dose of 300 mg/m² given every 3 weeks to adult patients with recurrent malignant glioma.

PATIENTS AND METHODS

Patient Selection

Patients 18 years of age or more were enrolled if they met the following criteria: (1) histologically confirmed primary malignant glioma that is progressive or recurrent as evidenced by contrast-enhanced magnetic resonance imaging (MRI); (2) previous radiotherapy or chemotherapy 4 weeks or more and prior surgical resection 10 days or more before study treatment; (3) Karnofsky performance status of 60% to 100%; (4) adequate organ function as documented by an absolute neutrophil count of more than 1,500/mm³, platelet count 100,000/mm³ or more, hemoglobin 9.0 g/dl or more, total bilirubin within normal limits, alanine transaminase and aspartate transaminase less than or equal to three times the upper limit of normal, and serum creatinine 2.0 mg/dl or less.

Patients were not eligible for the study if they had any of the following: (1) previous CPT-11 or topotecan treatment; (2) any active or uncontrolled infection; (3) psychiatric disorders that would interfere with consent or follow-up; (4) history of myocardial infarction within the previous 6 months or congestive heart failure requiring therapy; (5) history of prior malignancy except for adequately treated basal cell or squamous cell carcinoma or cervical carcinoma in situ, or other cancer for which the patient has been disease-free for at least 5 years; (6) pregnancy or lactation; and (7) any severe or concurrent disease that would make the patient inappropriate for study entry.

All patients were required to provide written informed consent as approved by local institutional review boards before initiation of any study procedures.

Treatment Plan

CPT-11 was supplied by Pharmacia & Upjohn, in 2-ml vials containing 40 mg of drug or 5-ml vials containing 100 mg of drug. CPT-11 was diluted with D5W to a total volume of 500 ml.

CPT-11 was administered as a 90-minute intravenous infusion once every 3 weeks at a starting dose of 300 mg/m². After 2 treatments, doses were increased to 350 mg/m² in those patients without grade III/IV toxicities.

Dose modifications were made for toxicity. If dose-limiting toxicities occurred, the dose was decreased by 50 mg/m² until the toxicities decreased to grade II or less. The following were considered to be dose-limiting toxicities: neutropenic fever, grade IV thrombocytopenia, grade IV diarrhea (despite intensive loperamide treatment), other grade III/IV nonhematologic

toxicities (except nausea/vomiting), and lack of recovery to baseline from previous toxicities.

Cholinergic symptoms occurring during or shortly after receiving CPT-11 could be treated with intravenous atropine (0.25–1 mg intravenously or as needed). Dexamethasone 10 mg intravenously was administered as part of the pretreatment antiemetic regimen unless a relative or absolute contraindication to corticosteroid use was identified. Additional antiemetic agents such as lorazepam, ondansetron, granisetron, and prochlorperazine were allowed. Loperamide was provided as therapy for delayed diarrhea. Patients were instructed to take 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. During the night, patients were allowed to take 4 mg every 4 hours. Routine prophylactic granulocyte colony-stimulating factor use was not recommended; however, it was allowed at the investigator's discretion.

Patients could be removed from the study for the following reasons: (1) documented disease progression after one or more courses; (2) unacceptable toxicity that did not respond to dose modifications; (3) withdrawal of patient consent; (4) intercurrent, non-cancer-related illness that prevented continuation of therapy or regular follow-up; (5) changes in the patient's condition, which in the investigator's opinion rendered the patient unacceptable for further treatment; and (6) failure to recover from CPT-11 toxicities to grade I or less or baseline by 5 weeks from the last prior CPT-11 therapy.

Study Evaluations

Four weeks before treatment, a medical history was taken and a chest radiograph was done. Pretreatment baseline tumor measurements were made by MRI within 4 weeks of treatment. Surgery was performed on patients in whom it was indicated for best clinical care and postsurgical baseline measurements of tumor size were made by MRI within 72 hours after surgery (performed with and without contrast). When surgery was performed just before initiation of therapy, all patients eligible for surgery had evidence of progression by MRI and were enrolled and signed consent before surgery. Two patients did not demonstrate evaluable tumor on the postoperative MRI scan.

Seven days before treatment, patients underwent a physical examination (including Karnofsky Performance Status, weight, and vital signs), neurologic examination, and a laboratory evaluation (complete blood count with differential, platelet count, serum electrolytes and chemistries, and pregnancy testing for women of childbearing potential).

At the beginning of each treatment course (week 1), patients underwent a physical examination (including Karnofsky Performance Status, weight, vital signs, and adverse event evaluation), neurologic examination, and a laboratory evaluation (complete blood count with differential, platelet, and serum electrolytes and chemistries).

During weeks 2 and 3 of each treatment cycle, patients had a complete blood count with differential. At 6 and 12 weeks after the first dose, and at least every 9 weeks thereafter until progression, an MRI of the brain was done with and without contrast. At the end of the study, a physical examination was done and the extent of the tumor was reevaluated with and without contrast. Adverse events were recorded for at least 30 days after the last treatment.

Tumor response was assessed according to modified World Health Organization criteria (i.e., complete response, partial response, stable disease (SD) 6 months or more, stable disease 6 months or less, and progressive disease [PD]). Complete

response was defined as the disappearance of all enhancing tumor on consecutive MRI scans at least 1 month apart, not taking steroids, and neurologically stable or improved. Partial response was defined as at least a 50% reduction in the size (product of largest perpendicular diameters) of enhancing tumor maintained for at least 1 month, with steroids stable or reduced, and neurologically stable or improved. SD was divided in two categories—one in which any change in tumor size that did not qualify for complete response, partial response, or PD lasted for 6 months or more and one that lasted for 6 months or less. PD was defined as at least a 25% increase in size (product of largest perpendicular diameters) of enhancing tumor or any new tumor on MRI scan, or neurologically worse, and steroids stable or increased. Patients who had a complete or partial response had a repeat tumor assessment in 4 to 6 weeks to confirm the initial response. After response confirmation, disease was reassessed at least every 9 weeks (or sooner if clinically indicated). In addition, time to tumor response, duration of response, time to tumor progression, and survival were measured.

Those patients in whom surgery was performed just before treatment and who had no contrast-enhancing residual disease were only allowed two response categories: PD (as described above but also including SD <6 months) and SD more than 6 months. This categorization was used to more effectively define positive responders in those patients without evaluable disease by MRI postoperatively.

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria.

Statistical Analysis

All eligible patients who received at least one course of chemotherapy were evaluable for efficacy. Patients who were removed from the study during the first course because of PD or serious drug-related events also were considered evaluable for efficacy. Patients removed from the study during the first course of treatment for other reasons (e.g., patient request or non-drug-related toxicity) were considered to be unevaluable for efficacy.

Time to tumor progression (time from start of therapy to first documentation of progressive disease) and survival (time from start of therapy to death) were analyzed by means of Kaplan-Meier analysis.

All patients who received any chemotherapy on this study were evaluable for safety. Adverse events were tabulated by frequency of occurrence.

RESULTS

Patient Characteristics

Fourteen patients were enrolled between August of 1997 and June of 1998. Patient characteristics are presented in Table 1. The median patient age was 39.5 years (range, 18–64 years). There were 11 men (79%) and 3 women (21%). Most patients (6/14, 42%) had a Karnofsky Performance Status of 90% to 100%. The majority of patients (12/14, 86%) had undergone prior surgery. Twelve patients (86%) had a histologic tumor classification of GBM and 2 patients (14%) had anaplastic astrocytoma. Half of the patients had tumors that were located in the frontal lobe. Two patients taking anticonvulsive medications (phenytoin and carbamazepine) had prior ni-

TABLE 1. Baseline patient characteristics (N = 14)

Characteristic	N (%)
Median age, y (range)	39.5 (18–64)
Gender	
Male	11 (79)
Female	3 (21)
Baseline performance status (Karnofsky)	
90–100	6 (42)
70–80	4 (29)
50–60	4 (29)
Prior debulking surgery	
With	12 (86)
Without	2 (14)
Histology	
Glioblastoma multiforme	12 (86)
Anaplastic astrocytoma	2 (14)
Tumor location	
Frontal	7 (50)
Temporal	5 (36)
Occipital	2 (14)

N, sample size.

trosoarea-based chemotherapy, and 1 patient taking valproic acid had no prior chemotherapy. All patients were taking enzyme-inducing antiepileptic drug (EIAED) except one who had taken valproic acid and gabapentin in combination.

Twelve patients had surgery within 3 weeks of initiating therapy to confirm tumor recurrence. These patients all showed histopathologic evidence of active tumor; all except two had evidence of contrast-enhancing tumor on the 72-hour postoperative scan. The 72-hour postoperative scan was used as the baseline for measuring tumor.

Treatment Administration

Fourteen patients received a total of 50 courses of treatment. The median number of courses administered was two (range, one to nine). Doses ranged from 250 mg/m² to 350 mg/m². Eight doses were delayed in four patients. Four of the doses were delayed because of grade II neutropenia and leukopenia, three were delayed because of grade II neutropenia, and one was delayed because of grade II thrombocytopenia.

Efficacy

Tumor response is presented in Table 2. All patients were evaluable for response. The objective response rate was 14% with 2 partial response, both in patients with GBM. One patient (7%) had SD for more than 6 months and 10 patients (79%) had PD. Time to tumor progression data were available for all patients. The median time to tumor progression was 6 weeks (range, 1–31 weeks). The median survival was 24 weeks (range, 1–81 weeks). The 1-year survival was 14%.

Safety

Safety results are summarized in Tables 3 and 4. There were no drug-related deaths. Grade III/IV adverse events

TABLE 2. Efficacy results

Endpoint	Result (N = 14)
Objective response rate	2 (14)
95% CI	1.8, 42.8
Complete response (n, %)	0
Partial response (n, %)*	2 (14)
Stable disease (n, %)	1 (7)
Progressive disease (n, %)	11 (79)
Time to tumor progression, median (range, wks)	6 (1–31)
6-Mo time to tumor progression (%)	14
Survival, median (range, wks)	24 (1–81)
1-Yr survival (%)	14

N, sample size.

* One response was confirmed ≥ 4 –6 weeks after first indication of partial response.

were infrequent and were limited to nausea (n = 1), vomiting (n = 1), and neutropenia (n = 2). Prolonged neutropenia developed in three patients that resulted in limiting dose escalation to 350 mg/m² or requiring dose reduction to 250 mg/m².

DISCUSSION

CPT-11 is approved for the treatment of colon cancer but is currently being investigated against a variety of other tumors.¹⁶ Its impressive activity against human GBM, medulloblastoma, and ependymoma xenografts in athymic nude mice suggests that it could be an important new addition to the therapy for central nervous system tumors.^{13,17}

An initial study¹⁵ of CPT-11 was conducted in patients with glioma who received a dose of 125 mg/m² for 4 weeks followed by a 2-week rest. The intent-to-treat response rate was 15% (95% CI, 6–24), and activity was observed in patients with GBM and anaplastic astrocytoma. Median overall survival was 43 weeks and 1-year survival was 33%. Toxicities were generally mild, with the frequency of grade III/IV toxicities lower than that observed in patients with colorectal cancer.¹⁰ A pharmacokinetic analysis was performed on 32 patients in the study and was compared with the previously determined pharmacokinetics observed in patients with colorectal cancer.^{10,18} Twenty-nine (91%) of the 32 patients with glioma were receiving anticonvulsant medications and

TABLE 3. Highest grade of nonhematologic adverse events by patient

Adverse event	Grade 0 N (%)	Grade I/II N (%)	Grade III/IV N (%)
Late diarrhea	9 (64)	5 (36)	0 (0)
Vomiting	8 (57)	5 (36)	1 (7)
Nausea	9 (64)	4 (29)	1 (7)

N, sample size.

TABLE 4. Highest grade of hematologic adverse events by patient

Adverse event	Grade 0 N (%)	Grade I/II N (%)	Grade III/IV N (%)
Neutropenia	7 (50)	5 (36)	2 (14)
Thrombocytopenia	10 (71)	4 (29)	0 (0)
Anemia	1 (7)	13 (93)	0 (0)

N, sample size.

all were receiving dexamethasone. No patients with colorectal cancer on whom pharmacokinetic studies were carried out were receiving these concomitant treatments. The results of the pharmacokinetic analysis showed that CPT-11 clearance was twice as high as that reported in patients with colorectal cancer: 30.4 \pm 8.3 l/hr/m² compared with approximately 13 l/hr/m². The AUC for CPT-11 in patients with glioma was approximately 40% of that determined in patients with colorectal cancer. The AUC values for the CPT-11 metabolites SN-38 and SN-38G were approximately 25% of those seen in patients with colorectal cancer.

Another study¹⁹ also determined that anticonvulsants increased the clearance of CPT-11 in patients with glioma. This study examined the pharmacokinetics of CPT-11 in 26 patients with recurrent glioma, of whom 20 were treated concurrently with corticosteroids and 23 were treated with anticonvulsants. Mean CPT-11 and metabolite AUC values for patients with glioma treated with anticonvulsants were 45% to 70% lower than those observed in patients with colorectal cancer.¹⁰

The results in both studies suggested that the pharmacokinetics of CPT-11 were altered by enzyme induction associated with the administration of anticonvulsant and corticosteroid drugs. Recent studies have shown this to be the case. In preclinical models, concurrent therapy with anticonvulsants and corticosteroids affected the pharmacokinetics of CPT-11 by inducing glucuronyl transferase enzymes, which resulted in a 72% enhancement in the AUC of SN-38G, a 31% reduction in the AUC of SN-38, and a 59% reduction in the AUC of CPT-11.²⁰ Dexamethasone, as well as anticonvulsants such as phenytoin, carbamazepine, and phenobarbital, can induce hepatic cytochrome P450 enzymes. Such induction could cause enhanced CPT-11 clearance and reduced concentrations of SN-38 and SN-38G. Such therapy could also enhance the biliary excretion of CPT-11 and its metabolites, potentially resulting in lower plasma concentrations.²¹

Our study evaluated a dose of 300 mg/m² of CPT-11 administered once every 3 weeks, which would hopefully be more "patient friendly" than 125 mg/m² every week times 4 weeks followed by a 2-week rest. It was anticipated that the higher dose might prove more beneficial to patients with glioma by resulting in higher peak plasma levels; however, the efficacy results in our study are consistent with those seen previously. The response

rate was 14% (95% CI, 2–43) and median survival was 24 weeks. Toxicities were similarly low. Grade III/IV neutropenia occurred in only 2 patients (14%). Nausea and vomiting occurred in only one patient (7%), and there were no cases of late grade III/IV diarrhea. No pharmacokinetic analysis was done in our study. However, the toxicity results suggest that, once again, concurrent use of anticonvulsants and dexamethasone resulted in lower than desired plasma levels of CPT-11 and SN-38 and in less toxicity.

These results suggest that a CPT-11 dosing regimen of 300 mg/m² to 350 mg/m² every 3 weeks is feasible and has activity against recurrent malignant, but that the maximum tolerated dose has not yet been reached. It is interesting that, in our sample, some patients on EIAED required dose deescalation predominately because of hematopoietic toxicities. This effect may be either because of prior chemotherapy exposure, or there may be unique interpatient pharmacogenetic differences with regard to CPT-11 metabolism. If higher doses could be tolerated, improved responses in this patient population could result. Further studies are planned in this same patient population at higher dose levels to evaluate safety and efficacy and to determine a maximum tolerated dose.



REFERENCES

- Pech IV, Peterson K, Cairncross JG, et al. Chemotherapy for brain tumors. *Oncology* 1998;12:537–47.
- Vecht CJ. Clinical management of brain metastases. *J Neurol* 1998;245:127–31.
- Oneschuk D, Bruera E. Palliative treatment of brain metastases. *Support Care Cancer* 1998;6:365–72.
- Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patient enrolled onto phase II clinical trials. *J Clin Oncol* 1999;17:2572–8.
- Yokokura T, Sawada S, Nokata K, et al. Antileukemic activity of new camptothecin derivatives. *Proceedings of the Japanese Cancer Association, 40th Annual Meeting, Sapporo, Japan*. 1981:228.
- Yokokura T, Furuta T, Sawada S, et al. Antitumor activity of newly synthesized, lactone ring-closed and water-soluble camptothecin derivative in mice. *Proceedings of the Japanese Cancer Association, 43rd Annual Meeting, Fukuoka Japan*. 1984:261.
- Kunimoto T, Nitta K, Tanaka T, et al. Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin, a novel water soluble derivative of camptothecin, against murine tumors. *Cancer Res* 1987;47:5944–7.
- Hsiang YH, Hertzberg R, Hecht S, et al. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J Biol Chem* 1985;260:14873–8.
- Hsiang YH, Liu LF. Identification of mammalian DNA topoisomerase I as an intracellular target of the anticancer drug camptothecin. *Cancer Res* 1988;48:1722–6.
- Camptosar brand of irinotecan hydrochloride injection [package insert]. Kalamazoo, MI, Pharmacia & Upjohn Co., 1997.
- Rothenberg ML, Kuhn JG, Burris HA III, et al. Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993;11:2194–204.
- Rivory LP, Riou JF, Haaz M-C, et al. Identification and properties of a major plasma metabolite of irinotecan (CPT-11) isolated from the plasma of patients. *Cancer Res* 1996;56:3689–94.
- Hare CB, Elion GB, Houghton PJ, et al. Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-(4-[1-piperidinol]-1-piperidino)-carbonyloxy-camptothecin against pediatric and adult central nervous system tumor xenografts. *Cancer Chemother Pharmacol* 1997;39:187–91.
- Colvin OM, Cokgor I, Ashley T, et al. Irinotecan treatment of adults with recurrent or malignant glioma [Abstract 1493]. *Proc Am Soc Clin Oncol* 1998;17:284a.
- Friedman HS, Petros WP, Friedman AH, et al. Irinotecan therapy in adults with recurrent or progressive malignant glioma. *J Clin Oncol* 1999;17:1516–25.
- Rothenberg ML. CPT-11: an original spectrum of clinical activity. *Semin Oncol* 1996;23:21–6.
- Nakatsu S, Kondo S, Kondo Y, et al. Induction of apoptosis in multi-drug resistant (MDR) human glioblastoma cells by SN-38, a metabolite of the camptothecin derivative CPT-11. *Cancer Chemother Pharmacol* 1997;39:417–23.
- Schaaf L, Tehhpurani N, Elfring G, et al. Influence of age on the pharmacokinetics of irinotecan (CPT-11) and its metabolites, SN-38 and SN-38 glucuronide (SN-38G) in patients with previously treated colorectal cancer [Abstract 708]. *Proc Am Soc Clin Oncol* 1997;16:202a.
- Reid J, Buckner J, Schaaf L, et al. Pharmacokinetics of irinotecan (CPT-11) in recurrent glioma patients: result of an NCCTG phase II trial [Abstract 540]. *Proc Am Soc Clin Oncol* 1999;18:141a.
- Gupta E, Wang X, Ramirz J, et al. Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. *Cancer Chemother Pharmacol* 1997;39:440–4.
- Rendie S, DiCarlo F. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. *Drug Metab Rev* 1997;29:413–80.