Phase I Study of Temozolomide and Irinotecan for Recurrent Malignant Gliomas in Patients Receiving Enzyme-Inducing Antiepileptic Drugs: A North American Brain Tumor Consortium Study

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Abstract

Purpose: To determine the maximum tolerated dose of irinotecan when administrated with temozolomide every 28 days, in patients with recurrent malignant glioma who were also receiving CYP450 enzyme-inducing antiepileptic drugs (EIAED), and to characterize the pharmacokinetics of irinotecan and its metabolites. The study was also intended to assess whether temozolomide affects the conversion of irinotecan to SN-38.

Design: Patients with recurrent malignant glioma received a fixed dose of temozolomide (150 mg/m^2) daily for 5 days from days 1 to 5 every 28 days, and an i.v. infusion of irinotecan on days 1 and 15 of each cycle. The starting dose of irinotecan was 350 mg/m^2, which was escalated to 550 mg/m^2 in 50-mg/m^2 increments. The plasma pharmacokinetics of irinotecan and its active metabolite, SN-38, were determined during the infusion of irinotecan on cycle 1, day 1.

Results: Thirty-three patients were enrolled into the study and treated. Thirty-one patients were evaluable for both tumor response and toxicity and two patients were evaluable for toxicity only. Common toxicities included neutropenia and thrombocytopenia, nausea, vomiting, and diarrhea. Dose-limiting toxicities were grade 3 diarrhea and nausea/vomiting. The maximum tolerated dose for irinotecan was determined to be 500 mg/m^2.

Conclusions: The recommended phase II dose of irinotecan in combination with temozolomide for patients receiving EIAEDs is 500 mg/m^2, administrated every 15 days on a 28-day schedule. This study also confirmed that concomitant administration of EIAEDs increases irinotecan clearance and influences SN-38 disposition. No pharmacokinetic interaction was observed between temozolomide and irinotecan.

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Despite advances in treatment, malignant gliomas carry a dismal prognosis. Even with aggressive treatment, consisting of surgery, radiation, and chemotherapy, the median survival time for patients with malignant glioma is only slightly >1 year, and <30% of patients survive 2 years (1). Temozolomide, an oral alkylating agent, has shown broad-spectrum antitumor activity against malignant gliomas *in vitro* (2–4). In preclinical studies, temozolomide showed high bioavailability after oral administration and good penetration into the central nervous system (5–7). The antineoplastic activity of temozolomide is thought to be primarily due to alkylation at the O^6 position of guanine, with additional nonlethal alkylation occurring at the N^7 position (8, 9). In phase I and II clinical trials conducted by the Cancer Research Council (United Kingdom), temozolomide showed antineoplastic activity in recurrent high-grade glioma, melanoma, and mycosis fungoides (9–11). These trials showed that temozolomide, when administrated orally daily for 5 days in a 4-week cycle, is well tolerated, with a low toxicity profile. Additional studies have confirmed these results and have extended these observations to the pediatric population

Table 1. Characteristic of the 33 patients enrolled into a phase I study of temozolomide and irinotecan

Total no. of patients	33
Sex	
Male	25
Female	8
Age (y)	
Median (range)	44.5 (21-66)
Karnofsky performance status score	
100	4
90	12
80	9
70	7
60	1
Median	80
Tumor pathology	
Glioblastoma	26
Anaplastic astrocytoma	5
Anaplastic oligodendroglioma	1
Gliosarcoma	1
Prior therapy	
Surgery	33
Radiation therapy	33
Chemotherapy regimens	10
One	7
Two	3

(4, 12, 13). Temozolomide has been evaluated in several phase II and III clinical trials for the treatment of malignant glioma and metastatic melanoma (14–16). Recently, the addition of temozolomide to radiation therapy for newly diagnosed glioblastomas resulted in a statistically significant survival benefit and conferred minimal toxicity; this combination, therefore, has become the first line treatment (17).

Irinotecan is a water-soluble chemical derivative of camptothecin, an alkaloid originally extracted from the Chinese tree, *Camptotheca acuminata*. It inhibits the topoisomerase-I enzyme which is essential for DNA replication, transcription, and repair (18, 19). Irinotecan is a prodrug; after parenteral administration, it is metabolized by carboxylesterase enzymes to form SN-38, a 1,000-fold more potent inhibitor of topoisomerase-I than irinotecan (20–23). SN-38 is further conjugated by uridine diphosphate glucuronosyltransferase to form a secondary metabolite, SN-38 glucuronide (SN-38G). Irinotecan was found to have activity against a panel of xenografts derived from pediatric and adult central nervous system tumors (3, 24), and thus, may be a suitable addition to other therapies for brain tumors. Clinical trials of irinotecan have been done in patients with recurrent malignant glioma (25–31). Initial pharmacokinetic studies indicated that the plasma concentration of irinotecan and SN-38 was lower and that the clearance was higher in patients receiving anticonvulsants. These findings suggested that antiepileptic drugs, known to induce hepatic cytochrome P450 enzymes (CYP450), may enhance the elimination of irinotecan, similar to the interaction noticed previously for 9-aminocamptothecin and paclitaxel (32). A phase I clinical trial confirmed that the concomitant administration of enzyme-inducing anticonvulsants in patients with recurrent glioma induced a marked enhancement in the clearance of irinotecan (27).

In preclinical studies, the combination of temozolomide and irinotecan showed enhanced activity in human glioma xenografts (33, 34). Based on these results, Gruber and Buster (35) conducted a clinical trial of the combination of temozolomide and irinotecan in 32 patients with recurrent malignant glioma. Twenty-two percent (5 of 18) of the patients with glioblastomas responded to the treatment [complete response (CR), 2; partial response (PR), 3].

In this report, we present the results of The North American Brain Tumor Consortium (NABTC) phase I trial of the combination of temozolomide and irinotecan, in patients with recurrent malignant glioma, who were receiving enzyme-inducing antiepileptic drugs (EIAED). Twenty-one patients were enrolled in the dose-escalation phase of this study, and received irinotecan from a starting dose of 350 mg/m^2, to a final dose of 550 mg/m^2. Twelve additional patients were treated in the extension phase of this study, in which the toxicity profile of irinotecan, at the maximum tolerated dose (MTD) of 500 mg/m^2, was characterized.

Patients and Methods

Study population and patient eligibility. Patients ages 18 year or older who had a histologic diagnosis of progressive or recurrent malignant glioma (glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, or mixed malignant glioma) were eligible to participate in this protocol. Patients were required to have measurable disease on contrast-enhanced computed tomography or magnetic resonance imaging, a Karnofsky performance status score of $\geq$60, and acceptable hematologic, liver, and renal function. The latter required an absolute neutrophil count of $\geq$1,500/mm^3, a platelet count of $\geq$100,000/mm^3, serum creatinine <1.5 mg/dL, serum bilirubin <1.5 mg/dL, and aspartate aminotransferase levels equal to or more than twice the institutional upper normal limits. All patients received EIAEDs. Patients were allowed to have three prior relapses, but they could not have undergone more than two prior chemotherapy regimens, including one prior adjuvant therapy and one prior regimen for recurrent tumor. The interval from the most recent prior irradiation or chemotherapy had to be at least 4 weeks (6 weeks if a nitrosourea-containing therapy had been used).

Patients were excluded if they were pregnant or breast-feeding, if they had severe nonmalignant systemic disease or active infection, or if they had an uncontrolled medical condition that, in the judgment of the investigator, would make the patient inappropriate for entry into this study. Patients who had received prior treatment with temozolomide or irinotecan were also excluded. All patients signed a written informed consent form approved by the institutional review board at each institution before treatment, informing them of the investigational

Table 2. Dose-escalation of irinotecan

Dose (mg/m^2)	No. of patients
350	6
400	3
450	3
500	6
550	2*
500	12 †

*These two patients developed grade 3 toxicity; thereafter, 12 additional patients were enrolled into the expansion portion of the study to further assess irinotecan toxicity.
† Expansion cohort.

Table 3. Reported dose-limiting toxicities

Toxicity	Irinotecan dose, mg/m^2 (no. of patients treated)					
	350 (6)	400 (3)	450 (3)	500 (6)	500 (12)*	550 (2)
Diarrhea	0	0	0	1	0	1
Granulocytopenia	0	0	0	0	0	0
Lymphocytopenia	0	0	0	0	0	0
Leukopenia	0	0	0	0	0	0
Nausea/vomiting	1	0	0	0	0	1

NOTE: No instances of grade 4 toxicity were reported.
*Expansion cohort of 12 patients accrued to further assess the irinotecan toxicity profile.

nature of this study. This phase I study was approved by the investigational review boards of all participating NABTC sites.

Treatment plan. All patients enrolled into the phase I study were receiving p450-inducing antiepileptic drugs, with or without steroids. The patients were not allowed to discontinue any EIAED during the investigational treatment, except for toxicity considerations. A treatment cycle was defined as the following: temozolomide 150 mg/m^2/d p.o. for 5 days from days 1 to 5, every 28 days, and irinotecan, at the specified dose, i.v. over a 90-min period on days 1 and 15, every 28 days. On day 1 of the first course of treatment, patients took the temozolomide in the morning, 2 h before the irinotecan infusion. On all subsequent days and cycles, temozolomide was given at the same dose, but was taken in the evening at the bedtime. There was no escalation of the temozolomide doses. The starting dose of irinotecan was 350 mg/m^2, and the dose was escalated to 550 mg/m^2 in increments of 50 mg/m^2. Cohorts of three patients were enrolled until dose-limiting toxicities (DLT) were determined. These patients were observed for DLT for at least 4 weeks from the first day of treatment, before new patients were enrolled to the next higher dose level. Standard phase I dose-escalation and MTD rules were used.

Patients remained on treatment until tumor progression, development of unacceptable toxicity, or completion of 12 cycles of temozolomide and irinotecan. The phase I extension portion of this study was initiated when the MTD was determined. At that time, 12 additional patients were enrolled at the MTD to further characterize the toxicity profile at this dose. The definition of DLT was based on the National Cancer Institute Common Toxicity Criteria Scale (NCI, 1999) and included the following:

- Hematologic toxicity: grade 4 neutropenia lasting >5 days, neutropenic fever (defined as grade 4 neutropenia with ≥grade 2 fever), neutropenic infection, or grade 4 thrombocytopenia.
- Diarrhea: grade ≥3, diarrhea despite maximal intensive loperamide support.
- Nausea or vomiting: grade ≥3 despite maximal antiemetic therapy. All patients were treated with dexamethasone (10 mg i.v.), and either ondansetron or granisetron before the infusion of irinotecan. Lorazepam or prochlorperazine were also allowed at the discretion of the treating physician. Patients were allowed to be premedicated with ondansetron (8 mg p.o.) 30 to 60 min before, and 8 h after temozolomide was given, to prevent nausea and vomiting.
- Other nonhematologic toxicity, including fatigue and alopecia: grade ≥3, attributable to irinotecan therapy.
- Failure to recover: failure to recover sufficiently from grade 3 or grade 4 toxicity to be eligible for re-treatment with irinotecan within 28 days of the start of the first cycle of irinotecan treatment.[15]

[15] https://webapps.ctep.nci.rih.gov/ctcv2/plsql/ctc000w.startup

Patient monitoring and toxicity assessment. A careful clinical evaluation which included complete physical and neurologic examinations, and determination of Karnofsky performance status was done every other cycle. Complete blood counts, including differential and platelet count, were obtained weekly throughout the course of treatment. Creatinine, blood urea nitrogen, total bilirubin, aspartate aminotransferase, and serum electrolyte level were determined prior to each cycle. Magnetic resonance imaging of the brain was done every other cycle to assess tumor response.

Temozolomide doses were held constant at 150 mg/m^2. Doses of irinotecan could be adjusted, according to the following criteria: at the end of each cycle, patients were assigned to receive either the same irinotecan dose at the next cycle (if they had stable disease), the same, or a reduced dose (if adverse events were encountered in the current cycle). If a patient experienced a DLT, the dose of irinotecan in subsequent cycles was reduced by one dose level (50 mg/m^2). Doses reduced for irinotecan-related toxicity were not re-escalated, even if minimal or no toxic effects occurred with the reduced dose. A new course of treatment could begin when the absolute neutrophil count was ≥1,500/mm^3, the platelet count was ≥100,000/mm^3, and any other treatment-related toxicities were grade 1 or lower. If toxicity was grade 2 or higher, treatment was deferred for 1 week; after the 1-week delay, if the toxicity was grade 1 or lower, then treatment resumed. If the toxicity was not resolved after 1 week, a second week's delay was allowed, but the treatment would resume with the irinotecan dose reduced by one level (50 mg/m^2). If the treatment had to be held off for >2 weeks, or if the administered dose would be <200 mg/m^2, the patient was removed from the study. Patients that had been removed from study because of irinotecan toxicity could continue to receive temozolomide off the study at the discretion of the treating physician. Because of the possibility of lacrimation, diaphoresis, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome in patients receiving irinotecan, i.v. or s.c. administration of prophylactic or therapeutic atropine was allowed.

Table 4. Number of responses by pathologic diagnosis

Tumor type	PR	CR	NC	PD
Glioblastoma	6	1	10	8
Anaplastic astrocytoma		1		3
Anaplastic oligodendroglioma			1	
Gliosarcoma				1
Totals	6 (19)	2 (6)	11 (36)	12 (39)

NOTE: Total number of patients assessed for response = 31.
Abbreviations: PR, partial response; CR, complete response; NC, no change; PD, progressive disease.

Table 5. Pharmacokinetic variables for irinotecan and SN-38 in patients also receiving EIAEDs at a dose of 500 mg/m^2

Pharmacokinetic variables	NABTC 9801 (32) irinotecan alone (n = 3)*	NABTC 9907 (current study) temozolomide and irinotecan (n = 6)
Irinotecan CL (L/h/m^2)	22.1	23.1
SN-38 AUC (ng × h/mL), dose normalized	0.46	0.31
SN-38/irinotecan (% ratio)	1.2	0.8

Abbreviation: CL, systemic clearance.
*Values reported are mean (±SD).

Patients were removed from the study if magnetic resonance imaging showed tumor progression, defined as a 25% increase in the sum of the products of measurable disease, or clear worsening of any evaluable disease, or the appearance of any new lesion. Failure to return for evaluation due to death or deteriorating condition was also coded as progression. Magnetic resonance imaging with volumetric analysis and results of neurologic examinations were used to determine response to therapy. Complete response required the complete disappearance of all measurable tumors, withdrawal from steroid treatment, and stable or improving neurologic function. Partial response was indicated by a reduction in tumor volume of ≥50%, with a stable or decreasing dose of steroids, and stable or improving neurologic function. Stable disease was defined by a clinical status and radiographic tumor measurements that did not meet the criteria for CR, PR, or progressive disease.

Pharmacokinetic evaluation of irinotecan. Heparinized blood (7 mL), was collected via peripheral venipuncture or through an indwelling central venous catheter heparin lock at the following times: prior to irinotecan administration (baseline), 45 min into the infusion, at the end of the infusion, and then 15, 30, 60, and 90 min, and 2, 3, 4, 6, 8, 10, and 24 h after the end of infusion on day 1 of a patient's first cycle, for a total of 14 samples per patient (31). Blood samples were centrifuged immediately after collection. Plasma was removed and frozen (≤-20°C) for subsequent analysis by high-performance liquid chromatography for total concentration of irinotecan and SN-38 (31). The total time of frozen storage was ≤1 year. Total concentrations of irinotecan and SN-38 in plasma are stable for at least 2 years, when samples are stored at ≤-20°C. The lower limits of quantification of irinotecan (expressed as the free-base, M_r 587) and SN-38 (expressed as the monohydrate, M_r 410) were 1 and 0.13 ng/mL, respectively.

Irinotecan and SN-38 plasma concentrations were analyzed by noncompartmental pharmacokinetic analysis methods. The maximal plasma concentration (Cp_{max}) of irinotecan was defined as the concentration observed at the end of the 90-min infusion. The Cp_{max} of SN-38 was determined by visual inspection of each individual's plasma concentration versus time profile. Elimination rate constants were estimated by linear regression of the last two data points on the terminal log-linear portion of the concentration-time curve. The terminal half-life ($t_{1/2}$) was calculated by dividing 0.693 by the elimination rate constant. The area under the plasma concentration-time curve was calculated using the linear trapezoidal rule up to the last measurable data point ($AUC_{0\text{-}24}$), and then extrapolated to infinity (AUC). The systemic clearance of irinotecan was determined by dividing the dose (in milligrams free-base of irinotecan per meter squared) by the AUC. A metabolic ratio, estimated as the ratio of $AUC_{SN\text{-}38}$ to $AUC_{CPT\text{-}11}$, was used as a measure of the relative extent of the conversion of CPT-11 to SN-38.

Statistical considerations. The primary end points of this phase I study were to characterize the toxicity and pharmacokinetics of irinotecan administered with temozolomide in patients taking EIAEDs and to define a recommended phase II dose of irinotecan. When the dose-escalation scheme described was used, the probability that the dose would be escalated to the next level, based on the true rate of the DLT at the current dose, was as follows: for a true toxicity of 10% at a given dose, the probability of escalating the dose was 0.91; for a true toxicity of 20%, the escalation probability was 0.71; at 30% true toxicity, the escalation probability was 0.49%; at 40% true toxicity, the escalation probability was 0.31; at 50% true toxicity, the escalation probability was 0.17; and at 60% true toxicity, the probability of escalating the dose was 0.08.

Table 6. Pharmacokinetic variable values for irinotecan, in patients who were and were not receiving EIAEDs

Pharmacokinetic variables	Values in patients not receiving EIAEDs NABTC 9801		Mean (±SD) values in patients receiving EIAEDs at the indicated irinotecan dose (mg/m^2)			
	200 (n = 20)	350 (n = 3)	400 (n = 4)	450 (n = 3)	500 (n = 6)	550 (n = 2)
CPT-11 (free base)						
Cp_{max} (μg/mL)	1.76 (±0.61)	2.83 (±0.43)	2.76 (±0.41)	3.31 (±0.67)	4.01 (±1.13)	3.57 (±0.11)
$t_{1/2}$ (h)	6.21 (±1.35)	4.67 (±0.39)	5.89 (±0.96)	6.06 (±0.47)	6.03 (±0.56)	5.57 (±0.73)
$AUC_{0\text{-}24}$ (μg × h/mL)	9.01 (±3.28)	12.38 (±1.46)	11.98 (±1.72)	13.36 (±5.49)	18.99 (±3.88)	17.53 (±5.67)
AUC (μg × h/mL)	9.42 (±3.43)	12.56 (±1.52)	12.44 (±1.93)	13.80 (±3.38)	19.58 (±3.94)	17.86 (±5.69)
CL (L/h/m^2)	20.31 (±11.15)	24.48 (±3.09)	28.48 (±4.45)	31.76 (±10.08)	23.05 (±5.09)	28.22 (±9.00)
SN-38						
Cp_{max} (ng/mL)	20.03 (±8.57)	27.24 (±11.15)	22.63 (±7.53)	17.22 (±11.77)	19.60 (±6.13)	17.94 (±13.10)
$t_{1/2}$ (h)	14.71 (±6.71)	9.04 (±3.10)	12.96 (±6.93)	11.75 (±3.13)	13.59 (±4.60)	12.71 (±14.65)
$AUC_{0\text{-}24}$ (ng × h/mL)	162.42 (±75.68)	167.91 (±68.46)	120.72 (±15.97)	106.12 (±45.30)	118.80 (±33.34)	134.99 (±107)
AUC (ng × h/mL)	254.10 (±34.49)	188.19 (±73.10)	157.90 (±37.84)	135.55 (±77.65)	153.13 (±45.16)	166.10 (±88.58)
$AUC_{SN\text{-}38}/AUC_{CPT\text{-}11}$ (%)	2.8 (±1.46)	1.5 (±0.44)	1.3 (±0.10)	1.0 (±0.12)	0.8 (±0.17)	1.0 (±0.21)

Abbreviations: CPT-11, irinotecan; CL, systemic clearance; Cp_{max}, maximal plasma concentration; $t_{1/2}$, terminal half-life (harmonic mean).

Pharmacokinetic variables are reported as mean values ± SD. Differences between the two groups with respect to kinetic variables were evaluated using an unpaired two-tailed (t) test. $P \leq 0.05$ was regarded as statistically significant.

Results

Patient characteristics. A total of 33 patients were enrolled in the phase I study (Table 1). There were 25 men and 8 women, with a median age of 44.5 years (range, 21-66), and median Karnofsky performance status score of 80 (range, 60-100). Twenty-six patients had glioblastomas, five had anaplastic astrocytoma, one had anaplastic oligodendroglioma, and one had gliosarcoma. Ten patients (nine with glioblastomas and one with anaplastic astrocytoma) had previously received chemotherapy (three patients had received two regimens and seven patients only one regimen).

Two patients were evaluable for irinotecan toxicity only, and not for tumor response. One developed dose-limiting grade 3 diarrhea at an irinotecan dose of 550 mg/m^2, and the other refused further treatment after the first cycle of chemotherapy. Thus, 31 patients were evaluable for both tumor response and toxicity. In the first group of three patients (with irinotecan administrated at a dose of 350 mg/m^2), one developed dose-limiting grade 3 nausea/vomiting; therefore, the next three patients (group 2) were enrolled at the same dose level. In the cohort of patients treated with an irinotecan dose of 500 mg/m^2 (group 5), one developed dose-limiting with grade 3 diarrhea; thus, three more patients were added at the same dose level (Table 2); none in the latter group developed a DLT. However, two patients from the next cohort, treated at a dose of 550 mg/m^2, experienced DLT. Thus, 500 mg/m^2 was declared the MTD, and 12 additional patients were enrolled into the extension portion of the study, to further characterize the toxicity profile. None of these 12 patients experienced DLT.

Toxicity. The dose of irinotecan ranged from 350 to 550 mg/m^2. DLTs were grade 3 nausea and vomiting, which occurred in one of six patients at the starting dose (350 mg/m^2) and grade 3 diarrhea despite maximal loperamide support, which occurred in one of six patients at the MTD (500 mg/m^2). Two patients were treated at the next dose level (550 mg/m^2), and both of them developed grade 3 toxicities (diarrhea in one patient and nausea and vomiting in the other). Table 3 describes the DLTs. Hematologic toxicities, reported during chemotherapy, included grade 3 neutropenia in 5 patients from the original cohort of 33 (15.1%). Two of these patients developed grade 3 neutropenia at an irinotecan dose of 400 mg/m^2, two at 500 mg/m^2, and one at 450 mg/m^2. One of the five patients developed a neutropenic infection at 500 mg/m^2. Grade 4 neutropenia was observed in only one patient at 500 mg/m^2. Grade 3 thrombocytopenia occurred in only one patient at 500 mg/m^2. Nonhematologic toxicity was primarily gastrointestinal: grade 3 nausea and vomiting occurred in three patients (9.3% of the original cohort) at 350, 450, and 500 mg/m^2. Grade 3 diarrhea occurred in two patients (6.0% of the original cohort) at 350 and 500 mg/m^2. One patient developed grade 3 liver toxicity with elevated bilirubin and hepatic enzymes levels at 500 mg/m^2: treatment was discontinued and the patient was removed from the study.

Five patients required a reduction in the dose of irinotecan during chemotherapy. Four of these patients developed grade 3 nonhematologic toxicities, including nausea, vomiting, and diarrhea; the DLT developed during cycle 1 in two patients, during cycle number 3 in one patient, and during cycle number 6 in the last patient. One patient developed grade 3 hematologic toxicity with neutropenic infection during cycle 8.

Of the 33 patients enrolled into the protocol, 3 completed 12 cycles of treatment. Two patients were discontinued from the study, one for grade 3 liver toxicity and one for grade 3 diarrhea; both continued chemotherapy regimen off-protocol. Two patients refused more treatment, after the first cycle, at the starting dose of irinotecan. Toxicity was not the stated reason for the patients' refusal, and both continued to receive temozolomide only off-protocol. No treatment-related deaths occurred in any of our patients. Based on the results of this phase I trial and the extension study, we recommend that a dose of 500 mg/m^2 be used in the phase II testing of irinotecan.

Tumor response. Thirty-one patients were evaluable for tumor response (Table 4). Eight patients (25.8%) achieved response to treatment (CR, 2; PR, 6), 11 (35.48%) remained stable, and 12 (38.7%) had progression of the disease. The two CRs, occurred at 450 and 500 mg/m^2. PRs were seen at 350 (n = 3) and 500 mg/m^2 (n = 3). Among the 25 patients with glioblastomas, 1 achieved CR, 6 achieved PR, 10 had stable disease, and 8 had tumor progression.

Pharmacokinetic results. Blood samples were collected from patients during their first course of treatment. Pharmacokinetic profile was determined for 18 patients treated with irinotecan at a dose range of 350 to 550 mg/m^2.

The pharmacokinetic results for these patients, all of whom were receiving EIAEDs at the time of temozolomide and irinotecan administration, were comparable to those of similar patients in our previous NABTC 9801 study evaluating single agent irinotecan (Table 5). The NABTC 9801 study was conducted in patients also receiving EIAEDs and compared the pharmacokinetics of irinotecan with those in patients not on EIAEDs therapy treated at the recommended phase 2 dose for other cancers. Table 6 summarizes the pharmacokinetic variables for irinotecan and its metabolite, SN-38. For the EIAED group, the relationship between irinotecan dose and systemic exposure (AUC) was relatively linear (r^2 = 0.74) over the dosage range of 350 to 550 mg/m^2. However, no dose-proportionate increase was observed in the SN-38 AUC. At the MTD of 500 mg/m^2, the AUC for irinotecan (19.58 μg × h/mL) exceeded the AUC (9.42 μg × h/mL) in the non-EIAED patients at the 200 mg/m^2 dose level, as shown in the previous study (Table 6). Nevertheless, the mean AUC for SN-38 at the MTD was 1.7-fold lower than the SN-38 AUC at the 200 mg/m^2 dose level for the non-EIAED patient group.

Discussion

This trial showed that this combination was generally well tolerated. The toxicity profile showed mainly low-grade hematologic effects, with grade 4 neutropenia occurring in only one patient. One patient developed a neutropenic infection. Nonhematologic toxicity was primarily gastrointestinal. Grade 3 liver toxicity occurred in one patient. The DLT at the 550 mg/m^2 dose level were grade 3 diarrhea and grade 3 nausea and vomiting. The recommended phase II dose of irinotecan in combination with temozolomide, in patients

receiving EIAEDs, is 500 mg/m^2, administrated on days 1 and 15 in a 28-day schedule.

Like previous studies, this clinical trial confirmed that EIAEDs have profound effects on irinotecan pharmacokinetics (10, 30). The pharmacokinetic variables for irinotecan and SN-38 in this analysis were similar to those reported in the previous NABTC 9801 clinical trial using irinotecan as a single agent every 3 weeks (Table 5). Irinotecan clearance was dose-independent. A relatively linear relationship (r^2 = 0.74) was observed between irinotecan dose and systemic exposure (AUC) over the dosage range of 350 to 550 mg/m^2. However, no relationship was found between irinotecan dose and AUC for SN-38. The mean AUC for SN-38 at the MTD was 1.7-fold lower than the SN-38 AUC at the 200 mg/m^2 dose level for the non-EIAED patient group. A low metabolic SN-38/CPT-11 ratio of 0.8 was determined for the EIAED group versus 2.8 for the non-EIAED group, which is in concordance with the results of the previous NABTC 9801 study of irinotecan as single agent in patients with malignant glioma. We also observed that SN-38 AUCs did not increase at irinotecan doses >350 mg/m^2 in the current study. Thus, it seems that the carboxylesterase enzyme may become saturated during the infusion of a relatively large, infrequent dose of irinotecan. An alternative route of elimination for the SN-38 metabolite, such as biliary elimination (MRP2 and MXR) or glucuronidation, is also a plausible explanation.

The objective response rate in our patients was 26% (8 of 31), including seven patients with glioblastomas (22.5%) and one patient with anaplastic astrocytoma (3.2%). The 6-month progression-free survival of >35% in recurrent glioblastomas led the Radiation Therapy Oncology Group to test this regimen up-front in newly diagnosed glioblastomas; that trial has completed accrual, and results are waited.

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