Effect of phenytoin on celecoxib pharmacokinetics in patients with glioblastoma

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Cyclooxygenase-2 (COX-2) expression has been linked to the prognosis, angiogenesis, and radiation sensitivity of many malignancies. Celecoxib, a selective COX-2 inhibitor, is predominantly eliminated by hepatic metabolism. This study was conducted to determine the effects of hepatic enzyme-inducing antiseizure drugs (EIASDs) on the pharmacokinetics of celecoxib. The safety of celecoxib administered with radiation for glioblastoma and the effect of the combined treatment on survival were also evaluated. Patients were stratified based on concomitant use of EIASDs. Celecoxib (400) mg was administered orally twice a day until tumor progression or dose-limiting toxicity. Standard radiation was administered without adjuvant chemotherapy. Sampling was performed to define the plasma concentration/time profile for the initial dose of celecoxib and steady-state trough concentrations. Thirty-five patients (22 +EIASD, 13 −EIASD) were enrolled. There were no significant differences in age, performance status, extent of surgery, or Mini Mental State Exam scores between the two cohorts. The treatment was well tolerated. All patients in the +EIASD arm were taking phenytoin. There were no significant differences in any celecoxib pharmacokinetic parameters between 15 +EIASD and 12 −EIASD patients. With 31 of 35 patients deceased, estimated median survival time for all patients was 12 months (+EIASD, 11.5 months; −EIASD, 16 months; $p = 0.11$). The pharmacokinetics of celecoxib is not significantly affected by the concomitant administration of phenytoin. Celecoxib administered during and after radiation is well tolerated. The potential difference in survival between the +EIASD and −EIASD groups deserves further evaluation. *Neuro-Oncology 10, 190–198, 2008 (Posted to Neuro-Oncology [serial online], Doc. D07-00050, February 20, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-055)*

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Cyclooxygenase-2 (COX-2) inhibitors hold promise in the prevention and treatment of cancer.[1–11] Cyclooxygenase exists in two isoforms: COX-1 is the constitutive form that is expressed in most tissues and has a homeostatic function, whereas COX-2 is inducible and is usually present in significant levels only in tissues when there is inflammation. Several studies have shown that COX-2 is overexpressed in many human tumors, including lung, colon, pancreatic, prostate, and

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glioma.[12–25] Because COX-2 is an inducible enzyme, it may be a suitable target for antitumor therapy. Cyclooxygenase catalyzes the rate-limiting step in the conversion of arachidonic acid to prostaglandins, which are believed to play a role in tumorigenesis. Specifically, prostaglandin E2 (PGE2) has been found to promote angiogenesis, inhibit apoptosis, and possibly protect cells against cytotoxic damage from radiation.[7,9,26]

Preclinical investigations have demonstrated that celecoxib, a selective COX-2 inhibitor, suppresses growth of lung and colon tumors in mice.[27] COX-2 is also upregulated in tumor cell lines after radiation, leading to increased levels of PGE2.[28] When a COX-2 inhibitor was added, such activity was suppressed. In mice bearing xenografts of U-87MG and U-251MG glioma cell lines, treatment with a COX-2 inhibitor reduced tumor cell migration and proliferation and increased apoptosis, suggesting that COX-2 may contribute to glioma tumorigenesis.[29] COX-2 protein has been noted in greater amounts in high-grade gliomas than in low-grade gliomas or normal brain, as has poorer survival in patients with malignant gliomas that have increased COX-2 expression.[29–36]

Studies of gliomas and other cell lines have demonstrated that COX-2 inhibitors are synergistic with radiation therapy.[37,38] Peterson et al.[38] conducted in vivo and in vitro studies examining the effect of COX-2 inhibitors alone and in combination with radiation in gliomas. Using a U-251MG cell line, a COX-2 inhibitor induced apoptotic death in approximately 90% of the cells and increased the sensitivity of the remaining cells to radiation. When U-251MG gliomas were implanted into the hind legs of nude mice, the administration of a COX-2 inhibitor slowed tumor growth compared to controls, and when it was combined with radiation, there was a greater than additive increase in tumor growth delay (9.9 days for radiation only compared to 25.4 days for radiation with the COX-2 inhibitor).

These preclinical data suggest that there is a potential role for COX-2 inhibitors alone or combined with radiation therapy in patients with primary brain tumors. However, prior to conducting formal efficacy trials to determine the impact of this class of agents, it is important to understand whether an interaction exists between COX-2 inhibitors and hepatic enzyme-inducing antiseizure drugs (EIASDs). Profound interactions between EIASDs and other therapeutic agents have been documented in patients with primary brain tumors.[39–49] Currently, little is known about the effect of EIASDs on the metabolism of celecoxib. The only available data derive from an unpublished report involving 16 healthy adults demonstrating that 1 week of treatment with celecoxib does not alter the pharmacokinetics of phenytoin and that a single dose of phenytoin does not affect the metabolism of celecoxib.[50] These data do not address the issues pertaining to the administration of celecoxib to patients with primary brain tumors chronically taking EIASDs.

The primary objective of this study was to determine the effect of EIASDs on the pharmacokinetics of celecoxib in patients with glioblastoma multiforme who are undergoing radiation therapy. This study also provided an opportunity to assess the safety of celecoxib and to obtain a preliminary estimation of its effect on the survival of patients with newly diagnosed glioblastoma receiving postoperative radiation. The results of this study describe the appropriate dose of celecoxib for subsequent clinical trials assessing the efficacy of celecoxib as a radiosensitizer in the treatment of primary brain tumors.

Patients and Methods

Patient Selection

Patients eligible for this study were 18 or more years of age with newly diagnosed, supratentorial glioblastoma multiforme and a KPS score of ⩾60. All patients were required to have recovered from surgery, to be on a stable dose of a corticosteroid for ⩾5 days, to have normal hematologic (absolute neutrophil count ⩾1,500/μl, platelet count ⩾100,000/μl, hemoglobin concentration ⩾9.0 g/dl), renal (serum creatinine ⩽1.7 mg/dl, calculated creatinine clearance ⩾60 ml/min), and liver (total bilirubin ⩽1.5 mg/dl, serum transaminases less than four times the upper limit of normal) function, and a Mini Mental State Exam score of ⩾15. Patients were ineligible if they had had another cancer within 5 years, peptic ulcer disease, allergy to sulfonamides, prior history of renal toxicity with nonsteroidal anti-inflammatory drugs, concurrent fluconazole therapy, or a contraindication to treatment with a COX-2 inhibitor. Patients were also excluded if they had received prior radiation or prior systemic or local chemotherapy for their brain tumor, were pregnant or breast-feeding, or had had another serious illness that would compromise their ability to receive protocol therapy. This study was approved by the Cancer Therapy Evaluation Program of the National Cancer Institute (Bethesda, MD, USA) and the institutional review boards of all participating institutions. Each patient signed a written informed consent document, satisfying all federal and institutional policies and regulations, as a condition of registering for participation in the study.

Treatment Plan

Patients were stratified into two groups, designated +EIASD and −EIASD, based on their concurrent use of antiseizure drugs. Patients in the +EIASD group were taking known inducers of hepatic drug-metabolizing enzymes, including phenytoin, carbamazepine, phenobarbital, primidone, and oxcarbazepine. Patients in the −EIASD group either were not taking an antiseizure drug or were using an agent that has not been shown to have a clinically significant influence on hepatic enzymes, such as gabapentin, lamotrigine, valproic acid, levetiracetam, tiagabine, topiramate, zonisamide, and felbamate. Celecoxib (Celebrex; Pfizer Inc., New York, NY, USA) was obtained commercially as 400-mg oral capsules. All patients received a single 400-mg dose of celecoxib orally 1 week prior to the start of conventional radia-

tion therapy. Beginning the following day, celecoxib 400 mg was given orally twice a day on a continuous basis until there was evidence of disease progression or treatment-related dose-limiting toxicity or the patient withdrew from the study. Radiation was administered to the tumor plus a generous margin to a dose of 6,000 cGy in 30 fractions using standard procedures and techniques employed in modern cooperative group brain tumor trials. Patients were followed with MRI every 2 months and for overall survival. Corticosteroids were used as clinically indicated to control peritumoral brain edema. Treatment with approved or investigational chemotherapeutic agents was not permitted.

Dose-Limiting Toxicities

For purposes of this study, the dose-limiting toxicities of celecoxib were defined as a creatinine clearance ≤60 ml/min or grade ≥3 gastrointestinal bleeding. If these occurred, subsequent dosing was to be held until toxicity receded, at which time therapy would be reinitiated with a 50% dose reduction. Furthermore, any 25% reduction in creatinine clearance or other grade 3–4 toxicities resulted in an immediate 50% dose reduction and discontinuation of therapy if the abnormalities did not subside within 2 weeks. If celecoxib was held for more than 2 weeks because of dose-limiting toxicities, the patient was taken off study. Seizures, other neurologic abnormalities, and thromboembolic disease were not considered dose-limiting toxicities for the purposes of this study unless the investigator felt the event was attributable to celecoxib. However, even events that were not considered dose-limiting toxicities were routinely recorded and reported to the New Approaches to Brain Tumor Therapy (NABTT) Operations Office so that their attribution could be readdressed if they were seen more commonly than expected.

Pharmacokinetic Studies

Blood specimens (7 ml) were drawn from a peripheral arm vein in tubes containing freeze-dried sodium heparin before dosing and at 0.25, 0.5, 1, 2, 3, 4, 6, and 24 h after the first dose of celecoxib. Samples were also collected shortly before dosing once a week during weeks 2–6. Sample tubes were mixed by inversion and placed over wet ice until centrifuged (1,200*g*, 10 min, 4°C) within 10 min. The plasma was stored at −70°C until assayed.

The concentration of celecoxib in plasma was determined by reversed-phase high-performance liquid with electrospray ionization mass spectrometric detection, as previously reported, with several modifications.[51] Briefly, frozen plasma samples were thawed at room temperature and mixed on a vortex stirrer. Plasma (50 μl) was mixed vigorously with 150 μl of acetonitrile containing the internal standard, bis(*N*-methyl)celecoxib, at a concentration of 0.2 μg/ml. The mixture was centrifuged for 5 min at 10,000*g* to sediment the precipitated protein. The supernatant (10 μl) was injected directly onto a 15 cm × 4.6 mm Luna 3 μm C18(2) high-performance liquid chromatography column (Phenomenex, Torrance, CA, USA), preceded by a 4 mm × 3 mm precolumn of the same stationary phase. The column was eluted with a binary mobile phase composed of acetonitrile and 25 mM ammonium formate in water delivered at 1.0 ml/min. The amount of acetonitrile was increased linearly from 60% at the beginning of the run to 85% over 10 min, held at 85% until the run ended at 11 min, and then decreased back to 60%. The column was permitted to reequilibrate for 3 min prior to the next run. Flow from the analytical column was directed without splitting into the electrospray ionization interface of the mass spectrometer. Nitrogen was used as the nebulizing gas at 35 pounds per square inch and as the drying gas at a flow rate of 9 liters/min and temperature of 350°C. The single-quadrupole mass spectrometer was operated in the selected-ion monitoring mode to measure positive ions corresponding to $[M+H]^+$ ions of celecoxib and the internal standard at *m/z* 382.1 and 410.1, respectively. Additional operating parameters were as follows: capillary potential, 5,500 V; mass width, 0.6–0.7 atomic mass units; dwell time, 289 ms; fragmentor potential, 200 V. The extracted ion chromatograms were integrated to provide peak areas.

Study samples were independently assayed in duplicate, on separate days, together with a series of nine calibration standards of celecoxib in human donor plasma at concentrations ranging from 25 to 2,500 ng/ml, drug-free plasma assayed with and without addition of the internal standard, and three quality control samples. Standard curves were constructed by plotting the drug/internal standard chromatographic peak area ratio against the known drug concentration in each calibration standard. Linear least-squares regression was performed with weighting in proportion to the reciprocal of the drug concentration normalized to the number of calibration standards. Values of the slope and *y*-intercept of the best-fit line were used to calculate the drug concentration in study samples. Specimens with concentrations exceeding the upper range of the standard curve were reassayed upon appropriate dilution with drug-free human plasma. The average of the two determinations of each study sample was calculated. Samples were reassayed in cases where the individual determinations differed from their average by more than 10%.

The analytical method was thoroughly validated according to current recommendations.[52] Retention times were typically 5.6 min (0.08 min peak width at half-height) for celecoxib and 9.2 min (0.10 min peak width at half-height) for the internal standard. Peaks that interfered with detection of the drug or internal standard were not evident in chromatograms of drug-free plasma from several anonymous donors and plasma samples obtained shortly before giving the first dose of celecoxib to patients participating in this clinical trial. Calibration curves exhibited excellent linearity with correlation coefficients ranging from 0.994 to 1.000. Interday accuracy of the assay for measuring 20 independently prepared sets of quality control samples of celecoxib in human donor plasma at concentrations of 75, 750, and 2,250 ng/ml over a 6-week period ranged

from 94.7% to 102.5% of the known concentrations, and the precision, calculated as the coefficient of variation, was 4.3%–8.0%. Accuracy and precision for measuring celecoxib at the 25 ng/ml lower limit of quantitation were 114.9% and 5.7%, respectively.

Actual sample times were calculated relative to the time that the first dose of celecoxib was taken. Celecoxib plasma concentration/time curves were analyzed by standard noncompartmental methods using WinNonlin Professional 5.0 software (Pharsight Corp., Cary, NC, USA).[53] Area under the plasma concentration/time curve (AUC) was estimated using the log-linear trapezoidal algorithm to the last data point, with extrapolation to time infinity using the estimated value of the slope of the terminal log-linear disposition phase (λ_z). Apparent oral clearance (CL/F) was calculated as the dose divided by the AUC, and the half-life of the apparent terminal phase ($t_{1/2,z}$) was calculated as $0.693/\lambda_z$. The steady-state minimum concentration of celecoxib in plasma (C_{min}^{ss}) was calculated for each patient as the geometric mean of the five determinations made before dosing on weeks 2–6. Observations were excluded if the sample was not collected within 12 ± 2 h after taking the prior dose, was drawn after dosing on the same day, or was determined to be an outlier by Dixon's test. C_{min}^{ss} was not calculated if there were fewer than three acceptable determinations.

Statistical Considerations

The study was nonrandomized, open label, and multicentered. Geometric means of the pharmacokinetic variables were calculated for each treatment group.[54,55] The jackknife technique was used to estimate the standard deviation of geometric means.[56] Mean pharmacokinetic parameters between the two treatment groups were compared using the two-tailed *t*-test after logarithmic transformation of the data. A difference of one standard deviation between mean pharmacokinetic parameters in the two treatment groups was considered to be clinically significant. Twenty-two patients in each group would be required to detect such a difference with a two-sided 5% significance level and power of 90%.[57]

Student *t*-test and the Fisher's exact test were used for comparison of baseline patient characteristics between the two groups. Survival time was measured from the time of histologic diagnosis to death due to all causes, or censored if a patient was alive at the time of last contact. Survival probability and median time of survival were estimated using the Kaplan-Meier method. Cox proportional hazard models were used to estimate the hazard ratio between the two groups. General data analyses were performed using SAS software, version 9.0 (SAS Institute, Cary, NC, USA). All p values were two-sided, and $p < 0.05$ was considered to be significantly different. No correction was made for multiple evaluations.

Results

Patient Characteristics

Baseline characteristics of the 35 patients who were enrolled in this trial from October 2003 to September 2004 are summarized in Table 1. The clinical trial was closed prematurely after preliminary results of the European Organization of Research and Treatment of Cancer (EORTC) trial became available documenting that temozolomide and radiation conferred a significant survival benefit in this patient population.[58] The median age of the patients was 57 years (range, 21–83), and the median KPS score was 90 (range, 60–100). Twenty-one were male, and 14 female; 30 were Caucasian, and 4 were African American. Thirty-one of the 35 patients had a formal craniotomy, whereas the other four had a biopsy only. One of the biopsy-only patients was in the +EIASD cohort, and three were in the −EIASD cohort. All 22 patients in the +EIASD group were receiving phenytoin. Five of the 13 −EIASD patients did not receive antiseizure drugs, and the remainder were taking levetiracetam ($n = 6$), lamotrigine ($n = 1$), or gabapentin ($n = 1$).

Treatment and Toxicities

Ten patients (28%) withdrew from the treatment for reasons other than disease progression or toxicity. Five of these patients were in the +EIASD group, and five were

Table 1. Patient demographic characteristics at baseline

Characteristic	+EIASD ($n = 22$)	−EIASD ($n = 13$)	p Value
Age, years [mean (± standard deviation)]	58 (±12)	56 (±17)	0.8
Gender [no. male (%)]	14 (64%)	7 (54%)	0.7
KPS score [mean (6 standard deviation)]	88 (±11)	83 (±9)	0.16
Corticosteroid therapy			
Yes	18 (82%)	11 (85%)	
No	4 (18%)	2 (15%)	1
Mini Mental State Exam score [mean (6 standard deviation)]	28 (±4)	28 (±3)	0.6
Prior surgery			
Craniotomy	21 (95%)	10 (77%)	
Biopsy	1 (5%)	3 (23%)	0.13

Abbreviation: EIASD, enzyme-inducing antiseizure drug.

in the −EIASD group. Reasons for withdrawal included refusal to continue (n = 4), poor compliance (n = 2), preference for another therapy (n = 3), and clinical deterioration (n = 1). Overall, the average time the patients received celecoxib was 116 days (±81 days), and the average duration of treatment was 117 days for the +EIASD group and 114 days for the −EIASD group (p = 0.59).

The approved dose and schedule of celecoxib were found to be well tolerated when administered to patients with newly diagnosed glioblastoma multiforme during and after standard radiation therapy. No significant renal insufficiency, gastrointestinal bleeding, or other major toxicities were observed. One patient had a dose reduction for a creatinine clearance of 59 ml/min, and one patient had a possibly related grade 3 hyponatremia when coming off study, so no dose reduction was applied. One patient had epigastric distress that responded to a dose reduction.

Pharmacokinetics

Pharmacokinetic data for the first dose of celecoxib were available for 15 patients in the +EIASD group and 12 patients in the −EIASD group. All of these patients were concurrently receiving stable doses of dexamethasone, with the exception of one patient in the +EIASD group and two in the −EIASD group. As illustrated in Fig. 1, the mean plasma concentration/time profiles for the first dose of celecoxib were very similar for both treatment groups. Fig. 2 shows values of the observed maximum concentration of celecoxib in plasma, the drug concentration in plasma 24 h after dosing, and the AUC from time 0 to 24 h after dosing for individual patients in both treatment groups. The distribution and range of individual values for each of these variables were comparable for patients in both groups, with no significant differences between the mean values. The mean and standard deviation for the celecoxib pharmacokinetic parameters determined for the two treatment groups are presented in Table 2. Differences between the mean pharmacokinetic parameters in the two groups were relatively small, ranging from 3.5% to 13.1% for all variables with the exception of C_{min}^{ss}, for which the difference was 35.8%. No differences between any of these parameters approached statistical significance. These findings suggest that the concurrent administration of phenytoin has no discernable effect on the plasma pharmacokinetics of celecoxib in this patient population.

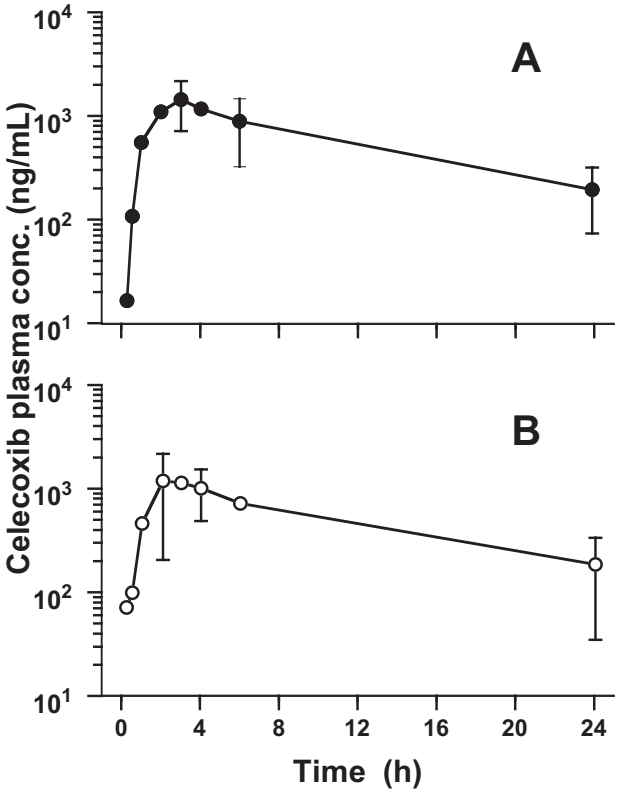

Fig. 1. Plots showing the mean plasma concentration/time profiles of celecoxib for all patients given enzyme-inducing antiseizure drugs (+EIASD treatment group (A) and those not given such drugs (−EIASD treatment group (B). Data points represent the geometric mean value in the group of patients with one standard deviation unit error bars at selected time points.

Survival

The survival analyses were based on all 35 patients who were enrolled into the study (Fig. 3). The latest survival data was obtained on May 30, 2006. Thirty-one (89%) of the 35 patients had died, 21 in the +EIASD group and

Table 2. Comparison of the mean (standard deviation) pharmacokinetic parameters for celecoxib between the two treatment groups

Parameter	+EIASD	−EIASD	Difference (%)	p Value[a]
No. of patients	15	12		
C_{max} (ng/ml)	1,813 (813)	1,752 (550)	3.5	0.82
C_{24} (ng/ml)	195 (122)	186 (151)	4.8	0.86
$t_{1/2,z}$ (h)	8.3 (3.8)	8.8 (2.7)	−5.7	0.72
AUC_{0-24} (ng·h/ml)	14,757 (7,013)	13,049 (6,074)	13.1	0.50
CL/F (liters/h)	22.3 (11.0)	25.1 (14.8)	−11.3	0.57
C_{min}^{ss} (ng/ml)	1,006 (476)	741 (367)	35.8	0.14

Abbreviations: EIASD, enzyme-inducing antiseizure drug; C_{max}, maximum drug concentration in plasma; C_{24}, drug concentration in plasma 24 h after dosing; $t_{1/2,z}$, apparent terminal-phase half-life; AUC_{0-24}; CL/F, apparent oral clearance; C_{min}^{ss}, steady-state minimum concentration of celecoxib in plasma.

[a]Two-tailed t-test of log-transformed data assuming unequal variances.

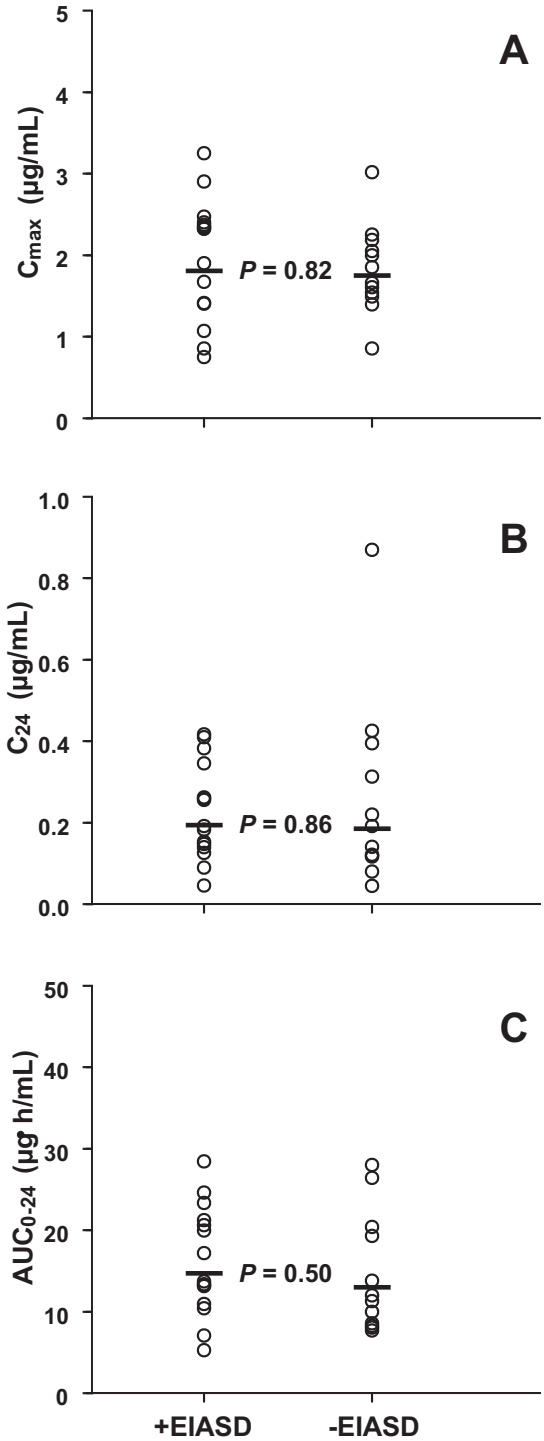

Fig. 2. Plot depicting the maximum drug concentration in plasma (A), the drug concentration in plasma 24 h after dosing (B), and the area under the plasma concentration/time curve from time 0 to 24 h (C) for the first 400-mg dose of celecoxib in patients given enzyme-inducing antiseizure drugs (+EIASD treatment group) and not given enzyme-inducing antiseizure drugs (−EIASD treatment group). Open circles represent the observed values in individual patients, and horizontal bars depict the geometric mean value for each group. Statistical comparison of the log-transformed data between the treatment groups was performed using a two-tailed *t*-test assuming unequal variances.

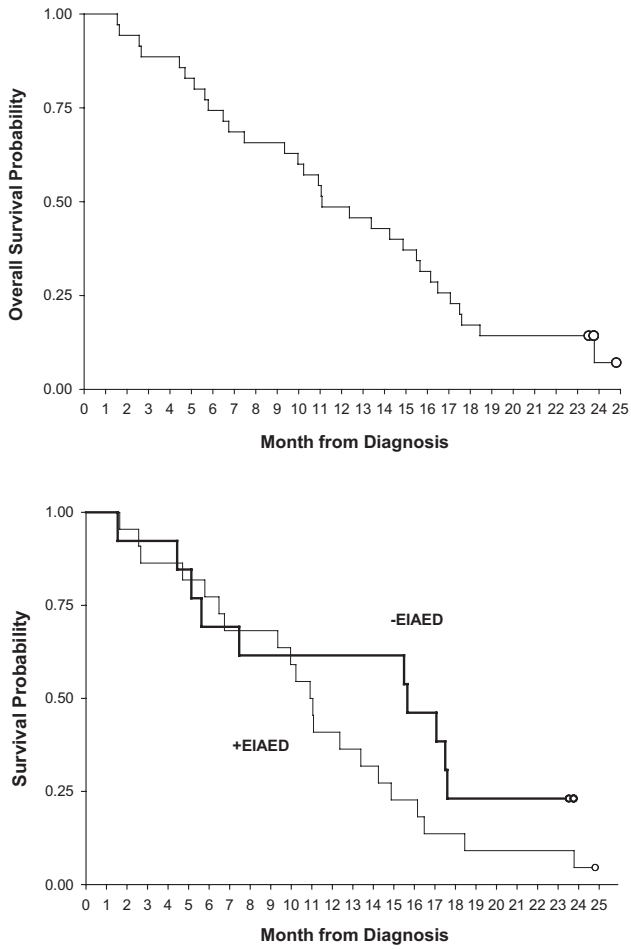

Fig. 3. Kaplan-Meier survival curves for all patients (top) and for patients who were (n = 22) and were not (n = 13) receiving enzyme-inducing antiseizure drugs (EIASDs; bottom). The overall median survival time was 12 months. Comparable figures for the +EIASD and −EIASD patients were 11.5 and 16.0 months, respectively (p = 0.11).

10 in the −EIASD group, with median follow-up time of 11 months (range, 1–25 months). The follow-up time was defined from the date that the patient started treatment to the last date known alive. The median survival time of all patients was 12 months (95% confidence interval [95% CI], 8–16 months). The median survival time of patients in the +EIASD group was 11.5 months (95% CI, 7–15 months), and in the −EIASD group, 16 months (95% CI, 6–18 months; p = 0.11). The hazard ratio for death in the +EIASD group compared to the −EIASD group was 2.7 (95% CI, 1.1–6.3) after appropriate adjustments for age and KPS score. Currently, three of the four patients alive are in the −EIASD group.

Discussion

The concurrent use of EIASDs can cause major alterations in the pharmacokinetics of many anticancer agents. As a result, studies such as the one described in this

report are needed to establish that adequate systemic exposure to novel agents is achieved before undertaking clinical trials to determine effectiveness in patients with primary brain tumors. Although celecoxib is predominantly eliminated by oxidative hepatic metabolism, the study reported here strongly suggests that the plasma pharmacokinetics of celecoxib are not affected by the concomitant administration of phenytoin. This finding is consistent with information from preclinical studies. In vitro studies have demonstrated that cytochrome P450 (CYP) 2C9 is the major enzyme catalyzing the hepatic metabolism of celecoxib, with metabolism by CYP3A4 being a relatively minor pathway.[59,60] The CYP isoenzymes induced to the greatest extent by phenytoin in human hepatocytes are 2B6 and 3A4.[61–64] However, dexamethasone is a very potent inducer of CYP2C9 in human hepatocytes, and 81% of the +EIASD patients and 86% of the −EIASD patients on this trial were receiving concurrent dexamethasone.[65] Nevertheless, the mean pharmacokinetic parameters of celecoxib determined in this study were very similar to previously published data in healthy adult volunteers who were not receiving concomitant glucocorticoids.[59,66]

This study also demonstrated that coadministering celecoxib to patients receiving dexamethasone to treat peritumoral brain edema was safe. No significant renal insufficiency, gastrointestinal ulceration, or bleeding was noted. Furthermore, no serious added toxicities were noted with the concurrent use of celecoxib and 6 weeks of involved field cranial irradiation.

A secondary objective of this study was to obtain preliminary data as to whether the addition of celecoxib affected patient survival. A total of 44 patients were to be accrued to make this estimate. However, when results became available documenting that radiation plus temozolomide improved survival, we felt that it was unethical to continue this study, which prohibited the addition of concomitant chemotherapy.[57] At this time, sufficient data were available to satisfy the primary pharmacokinetic objective of the study. As a result, this study was closed prematurely with a total enrollment of 35 patients. The overall median survival time for all patients was 12 months, which is what might be expected with radiation therapy alone. However, the 13 patients on the −EIASD arm of the study had a median survival time of 16 months, while that for the +EIASD patients was 11.5 months ($p = 0.11$). As noted in Table 1, the −EIASD and +EIASD patients had virtually identical ages ($p = 0.8$), performance status ($p = 0.16$), steroid requirements ($p = 1.0$), and Mini Mental State Exam scores ($p = 0.6$), and similar numbers underwent surgical debulking before radiotherapy ($p = 0.13$). It is difficult to attribute a potential survival advantage to celecoxib given the similar pharmacokinetics in the +EIASD and −EIASD patients unless the effect was due to a metabolite rather than the measured compound. Another possibility is that phenytoin imparts a negative impact on survival that is independent of celecoxib, which has been previously suggested.[67] Alternatively, this finding may be spurious, as the −EIASD cohort in this study contained only 13 patients. Although definitive conclusions cannot be derived from this study, this observation should be reexamined in future clinical trials of celecoxib in this patient population.

In summary, this report documents that there is no demonstrable pharmacokinetic interaction between either phenytoin or dexamethasone and celecoxib. Moreover, it documents that celecoxib can be safely administered to patients receiving cranial irradiation and dexamethasone for peritumoral brain edema. Although no overall survival benefit was noted in this small study combining radiation and celecoxib in patients with previously untreated glioblastoma, the outcome of −EIASD patients deserves further evaluation. These observations provide important preliminary data and set the stage for future trials evaluating combination therapy with radiation, temozolomide, and celecoxib in this patient population.

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