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A phase I/II trial and pharmacokinetic study of ixabepilone in adult patients with recurrent high-grade gliomas

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Abstract

Ixabepilone is an epothilone, a novel class of non-taxane microtubule stabilizing agents. A phase I/II and pharmacokinetic trial of ixabepilone was conducted in patients with recurrent high-grade gliomas. Adult patients received ixabepilone as a 1-h infusion daily for 5 days every 3 weeks. A modified continual reassessment method was used to escalate doses, beginning at 5.0 mg/m², in patients stratified by use or non-use of enzyme inducing antiepileptic drugs (EIAED). In the phase I study, the maximum tolerated dose (MTD) and pharmacokinetics of ixabepilone were

determined for each group. The phase II study used a two-stage design to evaluate response rate. Secondary endpoints were survival and 6-month progression free survival. In the phase I trial, 38 patients (median age 54 years) were enrolled. The MTD was 6.8 mg/m² for patients not taking EIAEDs and 9.6 mg/m² for those taking EIAEDs. The dose limiting toxicities in both groups were hematologic. Twenty-three patients (median age 54 years) were enrolled in the first stage of the phase II trial. No objective responses were observed. Median overall survival was 5.8 (95% CI, 5.0–8.6) months and 6-month PFS rate was 4% (95% CI, 0–22%). The overall mean total body clearance for ixabepilone was significantly higher ($P = 0.003$) in patients receiving EIAEDs (36 ± 11 l/h/m²) than those not (24 ± 9.2 l/h/m²). Patients on EIAEDs had a substantially higher MTD likely due to induction of cytochrome P450. Ixabepilone had no activity in patients with recurrent high-grade gliomas.

Keywords

Ixabepilone; Recurrent gliomas; Chemotherapy; Phase II

Introduction

Novel agents are needed to improve the survival and quality of life of patients with recurrent high-grade gliomas (HGGs) [1]. The epothilones are a novel class of non-taxane microtubule-stabilizing agents obtained from the fermentation of the cellulose-degrading myxobacteria *Sorangium cellulosum* [2]. These compounds induce polymerization of tubulin and enhance microtubule stability causing cell-cycle arrest at the G2/M transition with resultant apoptosis [3]. In addition, the epothilones have potent activity against paclitaxel-resistant cell lines encompassing both the multidrug resistance and the tubulin mutation modes of resistance [4].

Ixabepilone is a semi-synthetic analog of the natural product epothilone B [5]. Epothilone B, unlike paclitaxel, does not elicit endotoxin-signaling pathways in murine macrophages [6]. Therefore the production of proinflammatory cytokines and nitric oxide seen with paclitaxel has not been observed with epothilone B [3]. These preclinical data suggest that some adverse reactions seen with paclitaxel such as myalgias and arthralgias might not occur with ixabepilone.

Unlike paclitaxel, ixabepilone is not a substrate for p-glycoprotein. As p-glycoprotein is a major mechanism that impedes drug delivery across the blood–brain barrier (BBB), ixabepilone may demonstrate improved penetration of the BBB [7]. Prior clinical trials of paclitaxel demonstrated activity against HGGs with a response rate of 10–20% [8–10]. In addition, ixabepilone has activity against several pediatric brain tumor models [11]. Given the potential for improved activity and for improved BBB penetration compared with paclitaxel, a trial of ixabepilone against recurrent HGGs was initiated.

Ixabepilone may be a substrate for CYP3A4 in humans [12]. This metabolic pathway has particular relevance to patients with gliomas on anticonvulsants that interact with cytochrome P450 [13]. Due to the significant impact of these agents on the pharmacokinetics of many chemotherapeutic drugs, the phase I portion of this trial assessed the pharmacokinetics separately according to whether the patient was taking or not taking these agents. For patients with non-CNS malignancies the phase II dose had been established [14]. Nonetheless, a phase I trial in patients not taking enzyme inducing antiepileptic drugs (EIAED) was felt to be warranted as this patient population may differ significantly from patients with non-CNS malignancies by having a lower disease burden

and fewer prior regimens and therefore the potential to reach a higher maximum tolerated dose (MTD).

Ixabepilone has been tested on several schedules. Administration of this agent for five consecutive days every 21 days appears to decrease the incidence of neurotoxicity compared with other schedules [14]. The MTD on this schedule is 6 mg/m²/day with neutropenia as the dose-limiting toxicity (DLT) [14]. Antitumor activity has been seen against ovarian, cervical, colon, gastric, breast, melanoma, non-small cell lung cancers and non-Hodgkin's lymphoma [14–16]. Based on these considerations, a phase I/II trial of ixabepilone administered daily for five consecutive days every 21 days was initiated for patients with recurrent HGGs.

The primary objective of the phase I portion of this study was to establish the MTD of ixabepilone in adults with recurrent HGGs, receiving (+EIAED Group) or not receiving (–EIAED Group) anticonvulsants known to be metabolized by the P450 hepatic enzyme complex. The secondary objective of the phase I portion was to describe the pharmacokinetics of ixabepilone and to determine the effects of EIAED on the pharmacokinetics of this agent. The primary objective of the phase II portion of this study was to determine the radiographic response rate of adults with recurrent HGGs to ixabepilone when administered at the MTD. The secondary objectives were to determine the percent of patients with 6-month progression free survival (PFS) and to estimate median overall survival and PFS associated with this therapy.

Methods

This study was conducted by the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. The protocol for the study was reviewed and approved by the Cancer Therapy and Evaluation Program (CTEP) of the National Cancer Institute (Bethesda, MD, USA) and the institutional review board of each participating institution. Informed consent was obtained from each patient that participated. All patients eligible for this study were registered through the NABTT CNS Consortium's Central Operations Office in Baltimore, MD, USA.

Patient eligibility criteria

To be eligible for this study, patients were required to be at least 18 years of age with measurable, histologically proven anaplastic astrocytoma or glioblastoma multiforme which had progressed or recurred following radiation therapy and no more than two prior chemotherapy regimens. Patients with a previous low grade glioma and subsequent biopsy-proven HGG were also eligible. Patients were required to have measurable disease on MRI or CT within 2 weeks of starting therapy. Patients were required to have recovered from toxicity of prior therapies. The required interval from completion of the most recent therapy was 3 months for radiation and 3 weeks for chemotherapy (6 weeks for nitrosourea-containing chemotherapy). Patients were required to have a Karnofsky performance status $\geq 60\%$ and normal organ function as defined by absolute neutrophil count $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin >9 g/dl, creatinine ≤ 1.5 mg/dl, total bilirubin ≤ 1.5 mg/dl, and transaminases ≤ 2.5 times above the upper limits of the institutional norm. They were required to be maintained on a stable cortico-steroid regimen from the time of their baseline scan until the start of treatment and were required to have a Mini Mental State Exam score of at least 15. Patients were required to provide written informed consent and fertile patients had to agree to use acceptable birth control methods.

Exclusion criteria included pregnancy, breast feeding, concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the

cervix and breast. Patients with prior malignancies were required to be disease-free for at least 5 years.

Treatment plan

Patients received ixabepilone as a 1-h infusion daily for 5 days. Cycles were repeated every 21 days. No intra-patient dose escalation was allowed.

Phase I—dose escalation

Patients were assigned to one of two treatment groups (+EIAED and –EIAED) according to their use of cytochrome P450 enzyme-inducing antiseizure drugs. Dose escalation for each group occurred independently using a modified continual reassessment method (CRM) to estimate the MTD [17]. The starting dose level for both groups was 5 mg/m²/day. Cohorts of three patients received drug and were monitored for DLTs. Only toxicity associated with the first cycle of treatment was used for dose finding. All available toxicity data for a cohort were input into the CRM model to calculate the dose level associated with a predicted DLT rate of 33%, with the maximum increment permitted being 50% of the previous dose level. The entire process of modeling the data and re-estimating the MTD was repeated until the recommended dose was within 10% of the preceding dose for two consecutive iterations. This dose was declared the MTD.

Toxicities were graded according to the NCI Common Toxicity Criteria V.2.0. A DLT was defined as an ANC < 500/μl, platelets <25,000, febrile neutropenia or treatment-related grade 3 or 4 non-hematologic toxicity, with the exception of nausea, and vomiting.

Phase II—efficacy

The primary outcome of the phase II study was the objective response rate of the patients treated with ixabepilone at the MTD determined from the phase I study. Neurological examinations and MRI/CT scans were obtained prior to every odd cycle of ixabepilone to determine the response to therapy. A confirmatory scan was to be obtained at least 3 weeks after the initial complete or partial response. The 3 week interval for confirmation was chosen to coincide with the patient's return visit for the subsequent cycle of ixabepilone. A complete response was defined as complete disappearance of all tumor masses with resolution of all symptoms, physical findings and laboratory parameters related to the patient's disease while being off all steroids. A partial response was defined as a >50% decrease in the sum of the products of the perpendicular diameters of bidimensionally measurable lesions on stable or decreasing doses of steroids with stable or improving neurological symptoms or physical findings. Progressive disease was defined as new sites of disease or an increase of >25% in the sum of the products of the perpendicular diameters of bidimensionally measurable lesions on stable or increasing doses of steroids with stable or worsening symptoms and physical findings. Stable disease failed to meet the partial response and progressive disease criteria.

Dose modifications and off-study criteria

Dose reductions were required for any DLT which occurred during a previous course of treatment. The dose reduction was done by reducing the number of days the patient received treatment rather than by reducing the daily dose. Each dose reduction entailed one less day of drug administration (e.g., daily × 5 dosing was reduced to daily × 4 dosing).

Requirements for more than three dose reductions mandated removal of the patient from the study. Other off-study criteria included disease progression, patient refusal to continue treatment, a delay of treatment for greater than 2 weeks, or circumstances associated with further protocol therapy felt to pose an inordinate threat to the health of the patient.

No growth factors (G-CSF or GM-CSF) were to be used prophylactically in this protocol. Clinicians caring for patients on this protocol were permitted to use these growth factors to provide optimal care for patients with severe neutropenia in accordance with the ASCO guidelines. If these growth factors were used in the acute setting of neutropenia and infection (documented or suspected), they were not utilized prophylactically in subsequent cycles and were not used in lieu of dose reduction of ixabepilone.

Statistical considerations

The phase II trial employed a two-stage design intended to detect a 20% improvement in response rate over a background rate of 10% with type I and type II error rates of 5 and 10%, respectively. Specifically, a total of 22 evaluable patients were to be treated at the MTD in the first stage. If two or fewer patients showed evidence of response, the study was to be stopped. Otherwise, an additional 11 patients would be treated in the second stage. The treatment was to be recommended for further study if more than 6 of 33 patients responded after the second stage.

Secondary endpoints of the phase II trial included median overall survival, median PFS, 6-month PFS rate, and toxicities. Overall survival time was calculated as time from start of treatment until death from any cause. PFS was calculated as time from start of treatment until progression or death. Survival distributions were estimated using the product limit method. Frequency and percent of toxicities associated with ixabepilone treatment were calculated. SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC, USA) was used to perform analyses. Confidence intervals (CI) were calculated using standard methods. All analyses were intention-to-treat.

Pharmacokinetic studies

During treatment with the initial dose of ixabepilone, blood samples (7 ml) were drawn from a vein in the arm opposite to that used for infusing the drug and collected in tubes containing freeze-dried sodium heparin shortly before dosing, at the midpoint and just before the end of the infusion, and at 0.25, 0.50, 1, 2, 3, 4, 6 and 23 h after completing the infusion. Actual drug infusion and sample collection times were recorded. Sample tubes were placed on wet ice until centrifuged ($1800\times g$, 5 min, 4°C) within 15 min. The plasma was removed and stored at -70°C until assayed.

The concentration of ixabepilone in plasma was determined by reversed-phase high performance liquid chromatography with mass spectrometric detection. Analytical reference samples of ixabepilone and epothilone A, which was used as the internal standard (IS), were provided by Bristol-Myers Squibb Co. (New Brunswick, NJ). Study samples were thawed in a refrigerator and mixed by vortexing. Plasma (500 µl) was spiked with 5 µl of IS working solution (10 µg/ml in acetonitrile) and loaded onto a 3-cc Oasis HLB solid phase extraction cartridge (Waters Corp., Milford, MA) that had been preconditioned with methanol (3 ml) and water (3 ml). The cartridge was washed with 3 ml of methanol/10 mM ammonium formate (25:75, v/v), 3 ml of water, and eluted with 1.5 ml of acetonitrile. The solvent was evaporated and the extract reconstituted in *N,N*-dimethylformamide (75 µl) and 10 mM ammonium formate (75 µl). An autosampler with a refrigerated sample compartment (4°C) was used to inject 100 µl of the solution onto a 4.6 mm $\times$ 150 mm Luna 5 µm C18(2) HPLC column (Phenomenex, Torrance, CA). Chromatography was performed at ambient temperature using a binary mobile phase, delivered at 1.0 ml/min, composed of acetonitrile and 10 mM ammonium formate. The amount of acetonitrile was 48% from the beginning of the run to 3 min, then increased linearly to 95% over 2 min, and maintained at 95% for 5 min. Subsequently, the column was equilibrated with the initial composition of the mobile phase for 3 min before the next injection.

Flow from the column was directly introduced into the atmospheric pressure ionization-electrospray interface of an 1100 series ion trap mass spectrometer (Agilent Technologies, Palo Alto, CA). Nitrogen was used as the nebulizing gas at 50 p.s.i. and as the drying gas at a flow rate of 10 l/min and a temperature of 350°C. Operating parameters for the ion source and ion transfer optics providing optimal response for the $[M + H]^+$ ion of ixabepilone at m/z 507.3 were: capillary potential, -4500 V; skim 1, 20.57 V; capillary exit offset, 69.67 V; octopole, 3.03 V; octopole delta, 1.76 V; trap drive, 43.83 V; skim 2, -5.9 V; octopole rf, 300 V; lens 1, -1.43 V; lens 2, -30 V. Ion Charge Control was used to regulate the accumulation of ions in the trap (maximum accumulation time, 100 ms; maximum abundance, 30,000). Positive ion detection was performed in the normal scanning mode (m/z 400–600). Each data point in the total ion chromatogram was generated by averaging raw data from five scans with a rolling average of two scans. Extracted ion chromatograms for ixabepilone at m/z 507.3 and the $[M + H]^+$ ion of the IS at m/z 494.3 were integrated to provide peak areas.

Study samples were assayed in duplicate, on separate days, together with a series of eight calibration standards (1–100 ng/ml) and three quality control samples (3, 45, and 90 ng/ml) of the drug in human plasma. The relationship between the drug/IS chromatographic peak area ratio and the known drug concentration in each calibration standard was analyzed by linear least squares regression with weighting in proportion to the reciprocal of the squared 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. Samples were reassayed in cases where the individual determinations differed from their average by more than 20%.

The analytical method was thoroughly validated as recommended [18]. Typical retention times for ixabepilone and the IS were 3.8 and 6.0 min, respectively. Peaks that interfered with detection of the drug or IS were not evident in chromatograms of plasma from anonymous donors or plasma samples obtained shortly before the administration of ixabepilone from cancer patients participating in this clinical trial. Calibration curves exhibited excellent linearity with an average $\pm$ SD correlation coefficient of 1.0 ± 0.002 . Accuracy of the assay for measuring the quality control samples ranged from 96 to 103% and the precision was 9.0–16%. Accuracy and precision for measuring ixabepilone at the 1 ng/ml lower limit of quantitation were 92 and 17%, respectively.

Actual sample times were calculated from the beginning of the drug infusion to the sample collection time. Plasma concentration–time curves for individual patients were analyzed by standard noncompartmental methods using routines supplied in the WinNonlin Professional version 5.0 software package (Pharsight Corp., Cary, NC). Area under the plasma concentration–time curve (AUC) was estimated by the logarithmic-linear trapezoidal algorithm to the last data point, with extrapolation to infinity using the estimated value of the slope of the terminal logarithmic-linear data. Pharmacokinetic parameters estimated by the program included the total body clearance (CL), half-life of the terminal disposition phase ($t_{1/2,z}$), and the apparent volume of distribution at steady-state (V_{ss}). Pharmacokinetic parameters for groups of patients evaluated at each dose level are reported as the geometric mean $\pm$ SD of the individual patient values [19, 20]. Parametric statistical tests of pharmacokinetic variables were performed after logarithmic transformation of the data. All tests were two-sided and a value of $P < 0.05$ was the criteria for significance.

Results

Patient characteristics

Fifty-seven patients were enrolled in the phase I and II trial between October 2002 and November 2005. Demographic and clinical characteristics of the patients in each phase are presented in Table 1. Forty-four patients had undergone a debulking procedure at some time before entering this study; the remainder had been biopsied. All patients had received radiotherapy at least 3 months prior to study entry. Fifty-three patients had received chemotherapy either with or following radiotherapy. Ten patients had received nitrosoureas. The median number of prior chemotherapy regimens before study entry was 1 (0–2).

Phase I study: determination of the maximum tolerated dose

In the –EIAED arm of the study, three patients received the starting dose of 5.0 mg/m²/day with no DLTs. The CRM estimated the next dose level to be 7.5 mg/m²/day. One patient was treated at this dose level and died of neutropenic typhilitis (inflammation of the cecum) during cycle 1. Accrual to this cohort was stopped and the CRM was refit with these new data. After consultation with CTEP and study investigators it was decided to reopen the study at a dose level of 6.0 mg/m²/day and proceed with dose escalations. Three patients were treated at 6.0 and 6.6 mg/m²/day, and no DLTs occurred. At 7.0 mg/m²/day two of the three patients had DLTs (grade 4 ANC and grade 3 febrile neutropenia). The CRM estimated the next dose level to be 6.8 mg/m²/day, which was the second iteration within 10% of the previous level and therefore met criteria for the MTD. However, because the dose was higher than a previously tested safe dose, it was decided to evaluate this dose level. Four patients were accrued to the 6.8 mg/m²/day dose level because one patient had to be replaced because of early progression. One of the three evaluable patients experienced a DLT (grade 3 platelets not recovered within 2 weeks and grade 3 arthralgia) and 6.8 mg/m²/day was determined to be the MTD for the –EIAED arm of this study.

In the +EIAED arm of the study, no DLTs were observed at dose levels 5.0, 6.0, 7.0, 7.7, and 8.7 mg/m²/day of ixabepilone. One of the three patients treated with the next dose level of 9.6 mg/m²/day experienced dose-limiting neutropenia and another patient had a grade 2 toxicity. Because the CRM used all available toxicity data, it estimated the next dose level to be 9.5 mg/m²/day. Three patients were treated at this dose level with no DLTs. The next dose level was estimated to be 9.9 mg/m²/day, which met criteria for the MTD. However, because this dose level had not been tested and was such a small increase over the 9.6 mg/m² dose level, it was decided to declare 9.6 mg/m²/day as the MTD for the +EIAED arm.

Grade 3 or 4 toxicities felt possibly, probably or definitely related to therapy and that occurred in at least 5% of patients included: neutropenia (18%), leucopenia (14%), (hyper- or hypo-) phosphatemia (7%), and anemia (7%).

Median overall survival time for the patients on the phase I study was 5.9 months (95% CI, 3.6–9.6 months). One patient with stable disease was alive after 51 months of follow-up. There were no complete or partial responses in the 38 patients.

Phase II study: efficacy of ixabepilone

After the MTD of 6.8 mg/m²/day was determined for the –EIAED arm the phase II study was opened. The four patients treated at this dose level on the phase I study were included and nineteen additional patients were enrolled. There were no complete or partial responses. Consequently, the study was closed to further accrual. No patients who were concurrently receiving EIAEDs were enrolled in the phase II trial because the accrual goal was reached before the MTD was determined for the +EIAED arm. Median overall survival for the 23

patients was 5.8 months (95% CI, 5.0–8.6 months), and median progression free survival was 1.5 months (95% CI, 1.3–2.3 months). All of these patients have died and the 6-month PFS rate was 4% (95% CI, 0–22%).

Pharmacokinetics

Pharmacokinetic data for the first daily dose of ixabepilone was obtained for 13 of 21 +EIAED patients and 16 of 17 –EIAED patients. Mean values of the pharmacokinetic parameters for the cohorts of patients enrolled into each dose level are presented in Table 2 for both treatment groups. Linear pharmacokinetic behavior was supported by the absence of a significant correlation between the administered dose and the CL, V_{ss} , and $t_{1/2,z}$ of ixabepilone for patients in both treatment groups. Overall mean values of the pharmacokinetic parameters for both treatment groups of patients are listed and statistically compared in Table 3. The overall mean CL for ixabepilone was 50% greater in patients who received concurrent EIAEDs (36 ± 11 l/h/m²) than those who did not (24 ± 9.2 l/h/m²), which was statistically significant ($P = 0.003$). This difference in clearance was not associated with a change in the mean $t_{1/2,z}$, although the mean V_{ss} was 52% greater for patients in +EIAED group (440 ± 410 l/m²) than patients in the –EIAED group (290 ± 160 l/m², $P = 0.06$).

Discussion

This study determined that the MTD of ixabepilone in +EIAED patients (9.6 mg/m²/day) is substantially higher than the MTD in –EIAED patients (6.8 mg/m²/day) or in patients without CNS malignancies (6.0 mg/m²/day) [14]. There are several possible reasons why the MTD in the –EIAED group differed from the MTD in patients with systemic cancer. First, the dose escalation method, namely the CRM, differed from that in the trial of patients with systemic cancer. Second, the number of patients treated at each dose level in phase I trials is small enough that the differences in MTDs between two phase I trials may not be statistically different. Third, brain tumor patients usually have a lower overall disease burden and fewer prior regimens and therefore the potential to reach a higher MTD than those with systemic cancer.

The major toxicity in this study was hematological with neutrophil and platelet suppression. This phase I trial of ixabepilone did not reveal new toxicities in glioma patients with the possible exception of typhlitis for which ixabepilone could not be excluded as the cause. More likely, however, typhlitis was a complication of severe neutropenia rather than a toxicity caused directly by ixabepilone.

A recent study in which radiolabeled drug was administered to cancer patients established that hepatic metabolism is a major route of elimination for ixabepilone [21]. Unchanged drug accounted for only 19% of the AUC of the radioactive equivalent concentration of ixabepilone in plasma and 21% of the total radioactivity recovered in urine over a 7-day period. Ixabepilone is subject to oxidative metabolism in human liver microsomes catalyzed by cytochrome P450 3A4 (CYP3A4). CYP3A4 is the most abundant cytochrome P450 isoform in the human liver and mediates the metabolism of more than 50% of the drugs approved for clinical use [22]. The potential for a pharmacokinetic interaction should be considered whenever ixabepilone is administered together with other anticancer agents or supporting medications that either inhibit or induce CYP3A4. Indeed, a clinically significant interaction has been described in a preliminary report of a 78% increase in the AUC of the drug when given to patients who were pretreated with the CYP3A4 inhibitor ketoconazole [12].

Antiseizure drugs are frequently used in patients with primary brain tumors [23]. Many classical antiseizure drugs, such as phenytoin, phenobarbital, and carbamazepine, are potent inducers of various cytochrome P450 isozymes [24]. Marked interactions between EIAEDs and numerous anticancer agents have been documented in brain cancer patients [13, 25–34]. Therefore, a major objective of the pharmacokinetic studies undertaken during this clinical trial was to ascertain whether the concurrent administration of EIAEDs had any effect on the pharmacokinetics of ixabepilone. A majority of patients in the +EIAED dose escalation arm of the study were taking phenytoin, a well known inducer of CYP3A4 in primary human hepatocytes, and a significant effect on ixabepilone pharmacokinetics in these patients was observed [35–37].

The plasma pharmacokinetics of ixabepilone has been investigated in several phase I trials in which the drug was given alone to adult patients with advanced solid tumors [14, 38, 39]. In these studies, ixabepilone exhibited linear pharmacokinetic behavior at doses ranging from 3 to 56 mg/m² when given as a 1 h i.v. infusion. In patients treated with doses of 3–8 mg/m², which is similar to the range of doses evaluated in the present investigation, the mean CL of ixabepilone was 24 ± 7.6 l/h/m² [14]. This CL agreed closely with the overall mean CL for the 16 glioma patients who were not taking an EIAED (24 ± 9.2 l/h/m²). In contrast, the overall mean CL in glioma patients who were concurrently receiving an EIAED (36 ± 11 l/h/m²) was 50% greater ($P < 0.01$). The magnitude of the decrease in the CL of the drug is comparable to the difference between the MTDs in the two treatment groups.

Despite the attractiveness of this agent which is a weak substrate for p-glycoprotein and which has significant activity against taxane resistant-cells, ixabepilone had no demonstrable antitumor activity in this study of recurrent HGG. Although ixabepilone may be truly inactive in this disease it is also possible that therapeutic concentrations of this agent were not achieved in the tumor. Ixabepilone is a water soluble agent and has a molecular weight of 507 kDa which may impair its entry into gliomas with a relatively intact BBB. Furthermore, although ixabepilone is only a weak substrate for the p-glycoprotein efflux pump of the BBB, other transporters may promote efflux. Further studies of this or similar agents should evaluate intratumoral drug concentrations to determine if therapeutic levels can be achieved following intravenous administration.

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Table 1

Demographic and clinical characteristics

Characteristic	Phase I (n = 38)	Phase II ^a (n = 23)
Age in years, median (range)	54 (22–75)	53 (22–75)
Gender, male	28 (74)	13 (57)
Karnofsky performance status		
60%	5 (13)	0 (0)
70%	5 (13)	4 (17)
80%	9 (24)	5 (22)
90%	18 (47)	8 (35)
100%	1 (3)	6 (26)
Histology		
Glioblastoma multiforme	29 (76)	17 (74)
Malignant glioma, NOS	1 (3)	1 (4)
Anaplastic astrocytoma	8 (21)	5 (22)
Anticonvulsant use		
+EIAED	21 (55)	0 (0)
–EIAED	12 (32)	13 (57)
None	5 (13)	10 (43)

Frequency (%) reported unless otherwise noted

NOS not otherwise specified, *EIAED* enzyme inducing antiepileptic drugs

^aPhase II includes four patients that were also in the Phase I study

Table 2

Mean pharmacokinetic parameters for ixabepilone

Dose (mg/m ²)	No. of patients	C _{max} (ng/ml)	AUC (ng h/ml)	CL (l/h/m ²)	V _{ss} (l/m ²)	T _{1/2,z} (h)
+EIAED group						
6.0	3	52.3 ± 14.8	124.0 ± 41.4	48.4 ± 17.2	811 ± 459	17.8 ± 13.6
7.0	3	85.6 ± 5.4	184 ± 36.2	37.9 ± 7.6	376 ± 65	12.8 ± 1.1
7.7	3	114 ± 34.4	263 ± 67.0	29.3 ± 6.9	379 ± 342	14.4 ± 10.9
8.7	2	91.4 ± 9.5	233 ± 30.4	37.3 ± 4.9	314 ± 184	8.4 ± 4.0
9.6	2	123 ± 54.6	316 ± 68.8	30.3 ± 6.6	369 ± 210	11.6 ± 2.4
-EIAED group						
5.0	3	76.7 ± 50.5	200 ± 84.8	25.0 ± 9.8	235 ± 84	11.3 ± 2.6
6.0	3	106 ± 54.0	221 ± 12.7	27.2 ± 1.5	229 ± 169	11.4 ± 5.6
6.6	3	86.9 ± 19.1	214 ± 84.0	30.8 ± 13.5	395 ± 112	12.3 ± 4.6
6.8	3	75.8 ± 34.4	239 ± 65.4	28.5 ± 8.5	436 ± 179	14.8 ± 3.4
7.0	3	121 ± 27.8	392 ± 129	17.8 ± 5.4	241 ± 16	12.2 ± 2.9
7.5	1	329	628	11.9	181	14.4

Table 3

Comparison of overall mean pharmacokinetic parameters between the two treatment groups

Parameter	Treatment group		Difference (%)	P-value ^a
	+EIAED group	–EIAED group		
No. of patients	13	16		
T _{1/2, z} (h)	13 ± 11	12 ± 3.7	4.8	0.8
CL (l/h/m ²)	36 ± 11	24 ± 9.2	50	0.003
V _{ss} (l/m ²)	440 ± 410	290 ± 160	52	0.06

^aTwo-tailed *t*-test of log transformed data assuming unequal variances