

Plasma and cerebrospinal fluid pharmacokinetics of topotecan in a phase I trial of topotecan, tamoxifen, and carboplatin, in the treatment of recurrent or refractory brain or spinal cord tumors

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Abstract

Purpose This study was designed to ascertain the dose-limiting toxicities (DLT) and maximally tolerated doses of the combination of fixed-dose tamoxifen and carboplatin, with escalating doses of topotecan, and to determine the pharmacokinetics of topotecan in the plasma and cerebrospinal fluid.

Methods Tamoxifen 100 mg po bid, topotecan 0.25, 0.5, 0.75, or 1.0 mg/m²/d IV, administered as a 72 h continuous infusion on days 1–3, followed by carboplatin AUC = 3, IV on day 3. Cycles were repeated every 4 weeks.

Results Seventeen patients received 39 cycles of treatment: median 2, (range 1–5). The tumors included glioblastoma (6), anaplastic astrocytoma (2), metastatic non-small cell (3), small cell lung (2), and one each with medulloblastoma, ependymoma, and metastatic breast or colon carcinoma.

The median Karnofsky performance status was 70% (range 60–90%) and age: 52 (range 24–75). Eleven patients were female and six male. Toxicities included thrombocytopenia (2), neutropenia without fever lasting 6 days (1), DVT (2), and emesis (1). Topotecan levels, total and lactone, were measured prior to the end of infusion in plasma and cerebrospinal fluid (CSF). At 1.0 mg/m²/d, the median CSF/plasma ratio was 19.4% (range 15.1–59.1%). The total plasma topotecan in two pts with DLTs was 4.63 and 5.87 ng/ml, in three without DLTs at the same dose level the mean total plasma topotecan was 3.4 ng/ml (range 3.02–3.83). Plasma lactone levels were 33% of the total; CSF penetration was 20% of the total plasma levels. 4/8 pts with high-grade gliomas had stable disease (median: 3 cycles (range 2–5)). Two had minor responses. One patient with metastatic non-small cell and one with small cell lung cancer had objective PRs.

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Conclusions The recommended phase II doses are: tamoxifen 100 mg po bid, topotecan 0.75 mg/m²/d IV continuous infusion for 72 h, followed by carboplatin AUC = 3 IV on day 3. Measurable topotecan levels, both total and lactone, are observed in the CSF.

Keywords Topotecan · Carboplatin · Tamoxifen · Brain tumors · Chemotherapy

Introduction

The diagnosis of primary or metastatic central nervous system tumors carries a grim prognosis. Median survivals for high-grade primary glial tumors range from 11 to 33 months at the time of primary diagnosis, and 7 months following recurrence [1]. The median survivals of patients with metastatic epithelial neoplasms range from four to 14 months with the best available therapy [2]. Patients with recurrent tumors following radiation have few options.

Systemic single agents, including carboplatin, topotecan, and tamoxifen, have been used to treat primary or metastatic brain tumors [3–12], and the combination of tamoxifen or topotecan, a topoisomerase I inhibitor, and platinum-based agents have been shown to be synergistic [13–15]. Based on these pre-clinical and clinical observations, we designed a phase I trial to determine the dose-limiting toxicity and maximally tolerated doses of the combination of tamoxifen, carboplatin and topotecan in patients with recurrent primary or metastatic brain tumors. This study was designed to take advantage of the known single agent activity of each of these agents, and to exploit the synergistic activity that has been shown for tamoxifen/platinum and platinum/topotecan combinations. Cerebral spinal fluid analysis allowed greater understanding of the ability of topotecan to penetrate the blood–brain barrier.

Patients and methods

Patient selection

Between June, 1999, and September, 2001, 17 patients with advanced or recurrent histologically proven primary or metastatic central nervous system malignancies were entered on this phase I trial. The tumor must have been unresponsive to previous chemo- or radiotherapeutic regimens, or have no defined “standard” chemotherapeutic regimen. Patients were required to have a Karnofsky performance status of greater than or equal to 50% and age greater than or equal to 18 years, and an expected survival of at least 1 month. Adequate renal function was defined as serum creatinine ≤ 1.5 mg/dl. Adequate bone marrow func-

tion for enrollment was defined as a total white count $\geq 4,000/\mu\text{l}$ or absolute neutrophil count $\geq 2,000/\text{dl}$, and platelet count $\geq 150,000/\mu\text{l}$. Adequate hepatic function was defined as serum bilirubin ≤ 1.5 mg/dl, and SGOT and SGPT within twice the institutional upper limit of normal. Prior radiation or chemotherapy must have been completed at least 4 weeks prior to beginning treatment on this protocol. Ongoing steroid or anti-convulsant therapy was not an exclusion for entry on this study; however, patients must have been on a stable dose for 2 weeks prior to beginning therapy. There was no limit on the number of prior courses of chemotherapy or radiotherapy. Female patients could not be pregnant. All patients gave their voluntary informed consent and signed a consent document that had been reviewed and approved by the City of Hope National Medical Center Clinical Protocol Review Monitoring Committee and Institutional Review Board.

Pretreatment evaluation

All patients had a complete history and physical examination including documentation of weight, Karnofsky performance status, and the presence of measurable or evaluable disease.

Additionally, a complete blood count with platelet count and differential, 18 channel blood chemistry analysis, serum magnesium level, pregnancy test (if indicated), and appropriate radiographic examinations (either computed tomographic exams or magnetic resonance imaging) were performed as needed to document measurable or evaluable disease and evaluate responses to therapy. All patients who were medically eligible underwent a cerebrospinal fluid examination via lumbar puncture or Omayya reservoir (one patient) immediately prior to the completion of the topotecan infusion. The fluid was evaluated for cell count, differential, cytological examination, and topotecan levels. Patients with measurable disease were required to have radiographic procedures for analysis of measurable disease repeated no more often than every 8 weeks.

Treatment plan

This trial was designed as a phase I study of oral tamoxifen 100-mg bid starting on day 1, followed by a 72-h infusion of topotecan at escalating doses (see Table 1), followed by

Table 1 Number of courses completed

Dose level	Topotecan dose (mg/m ² /d)	Courses (# pts)
1	0.25	8 (3)
2	0.5	8 (3)
3	0.75	13 (6)
4	1.0	10 (5)

a fixed dose of carboplatin ($AUC = 3$) at the end of the topotecan infusion. The initial dose of topotecan was $0.25 \text{ mg/m}^2/\text{d}$ with subsequent dosage increases to 0.5, 0.75, and $1.0 \text{ mg/m}^2/\text{d}$ for 72 h. The carboplatin dosage for cycle 1 was determined by using a measured creatinine clearance and for subsequent cycles by using the calculated creatinine clearance. Cycles were repeated every 4 weeks.

Patients were treated in cohorts of three. The starting dose of intravenous topotecan was determined by decreasing the usual intravenous dose by approximately 80% and subsequently escalating according to a modified Fibonacci scheme. (Table 1).

Patients experiencing any grade 3 toxicity were allowed to receive subsequent cycles of therapy at a dose reduction of one level. If a second grade 3 or any grade 4 toxicity was observed on a subsequent cycle, the patient was taken off study. A minimum of three evaluable patients were entered at each dose level. Dose level escalations were determined by the toxicity encountered after the first cycle of chemotherapy. If after one complete course of therapy there were no grade 3 or 4 toxicities observed in any member of the cohort, the dosage of topotecan was escalated by one level. A single instance of grade 3 toxicity resulted in the accrual of three additional patients at that dose level. Dose escalation continued until grade 3 or 4 toxicity was observed. If no further grade 3 toxicities were observed in the additional patients, drug doses were escalated to the next level. A single instance of grade 4 toxicity at any dose level or a second grade 3 toxicity in the additional three patients established the maximally tolerated dose to be one dose level lower (i.e.: the dose at which no grade 4 toxicities and at most one grade 3 toxicity were encountered in a six-patient cohort). Standard response criteria were used in patients having measurable or evaluable disease [16]. Toxicity was measured using the Common Toxicity Criteria of the National Cancer Institute, Version 2.0, 1/30/98.

Plasma and cerebrospinal fluid sampling

Peripheral blood samples were collected in heparinized (green-top) tubes and immediately placed on ice at the following times during cycle 1: immediately prior to the start of the infusion, then at 24, 48 and 72 h during the infusion. Plasma was separated from whole blood and processed within minutes of drawing to minimize the *ex vivo* conversion of the topotecan lactone to the carboxylate form. Processing for the topotecan lactone form consisted of adding $100 \mu\text{l}$ plasma to $300 \mu\text{l}$ very cold methanol ($<-70^\circ\text{C}$). The resulting protein precipitate was pelleted by centrifugation, and the methanolic supernatant was decanted and stored in polypropylene tubes at -70°C until analysis. Following processing for lactone levels, any remaining plasma was

stored at -70°C for subsequent determination of total topotecan levels (lactone + carboxylate). Prior to assaying for total topotecan concentration, the plasma samples were acidified with concentrated phosphoric acid to convert the carboxylate to the lactone form.

Cerebrospinal fluid measurements of topotecan (in patients medically able to have a lumbar puncture) were performed immediately prior to the end of the topotecan infusion with the first course of treatment only. The CSF samples were processed for lactone, and total topotecan levels in an identical manner to the plasma samples as described earlier.

Pharmacologic analysis of topotecan

Total topotecan and the lactone form in plasma and CSF were measured according to a modification of a previously described HPLC assay method [17]. Briefly, the assay involves reversed phase separation of topotecan from interfering compounds in plasma across a Waters $150 \times 4.6\text{-mm}$ C18 analytical column (Milford, MA) and fluorescence detection using an excitation wavelength (λ_{ex}) of 381 nm and an emission wavelength (λ_{em}) of 527 nm. Data were collected and analyzed using Shimadzu Class-VP software (version 5.4). All HPLC instrumentation was purchased from Shimadzu Corporation (Columbia, MD), and all mobile phase reagents were of analytical grade purchased from Sigma Chemical (St. Louis, MO). Inter- and intra-day precision and accuracy of the assay method is $<10\%$, and the limit of quantitation is 0.25 ng/ml .

Statistical considerations

This study was designed as a phase I trial designed to establish the maximally tolerated dose and the dose-limiting toxicity of the combination of tamoxifen, carboplatin, and topotecan when administered on this schedule. The dosing schema is outlined in Table 1. To be evaluable for toxicity, a patient must have received at least one course of treatment and been observed at for at least two weeks after the first course or have experienced DLT.

Results

Patient characteristics

Seventeen patients received 39 cycles of treatment on this phase I trial. (see Table 1). Eleven patients were female and six were male (Table 2). The median age was 52 years (range 24–75), and the median Karnofsky performance status was 70% (range 60–90%). The tumor types included: glioblastoma multiforme (6), anaplastic astrocytoma (2),

Table 2 Patient characteristics

Gender	
Female	11
Male	6
Race	
Caucasian	14
Asian	2
African-American	1
Karnofsky	
90–100	4
70–80	9
60	4
Histologic types	
Glioblastoma multiforme	6
Anaplastic astrocytoma	2
Ependymoma	1
Medulloblastoma	1
Metastatic carcinoma	7
Age in years [median (range)]	52 (24–75)

Table 3 All regimen related grade 3/4 toxicity

Toxicity	# Episodes
Hematologic	
Granulocytes <1,000/ μ l	5
Platelet nadir <50,000/ μ l	6
Requiring transfusion	3
Nausea/vomiting	
Intractable (grade 3)	1
Venous thrombosis	2

ependymoma (1), medulloblastoma (1), and metastatic non-small cell lung (3), small cell lung (2), breast (1), and colon (1) carcinomas. All patients had received prior surgery and radiotherapy. Twelve patients had received prior chemotherapy. Nine patients received concurrent enzyme-inducing anti-epileptic drugs.

Dose-limiting toxicities of therapy

The toxicities attributable to the chemotherapeutic regimen are summarized in Table 3 and were overall quite mild. Dose-limiting toxicity was noted in two patients at dose level 4 (1.0 mg/m²/d). One patient experienced grade 4 thrombocytopenia, and one other patient experienced uncomplicated grade 4 neutropenia persisting for 11 days. At dose level 3 (the maximally tolerated dose), two patients of six experienced deep venous thromboses with pulmonary emboli.

One of these was felt to be regimen related; the other, however, occurred in a patient who had a rapid decline in

Table 4 Responses to therapy

Response	No. of patients	Dose levels
Partial response	2	3,4
Minor response	2	1,2
Stable disease	4	1,2
Progression	8	1,2,3
Inevaluable	1	4

performance status due to disease progression and was felt to be due to the underlying disease process. One patient experienced severe nausea and vomiting. No dose-limiting toxicities were noted in the first two dosage levels.

Best responses, and reasons for discontinuation of protocol therapy

The best responses noted on this study are summarized in Table 4. Two patients were observed to have objective partial responses in the brain, one with small cell and one with non-small cell lung carcinoma. These two patients progressed systemically while maintaining CNS response following two and five courses of therapy. One patient with glioblastoma who received five courses of chemotherapy and one patient with anaplastic astrocytoma who received two courses of chemotherapy had minor responses with markedly decreased gadolinium enhancement observed on serial MRI scans. These two patients discontinued treatment due to lack of clinical improvement despite radiographic response. Four patients had stable disease for a median of 3 courses of chemotherapy. One of these progressed following the third course of therapy, two declined clinically despite radiographic stability, and one experienced grade 4 myelosuppression mandating removal from protocol therapy. Eight patients progressed following a median of one course of treatment. The median survival for all patients entered on this trial was 5.5 months (range 1–33 months).

Pharmacokinetics

Plasma and cerebrospinal fluid pharmacokinetic analyses for topotecan were performed on fifteen patients and are summarized in Table 5. The mean peak plasma concentration at the maximally tolerated dose of 0.75 mg/m² was 2.74 ng/ml. The lactone portion was 0.54 ng/ml, representing 23.2% of the total plasma topotecan. The total cerebrospinal topotecan concentration at that dose level was 0.76 ng/ml, representing 21.8% of the peak plasma concentration. CSF lactone levels were measurable in one patient at dosage level 4 and represented approximately 50% of the total CSF topotecan concentration.

Table 5 Topotecan pharmacokinetics

Dose level (mg/m ²)	Plasma total (ng/ml) (No. Pts)	Plasma lactone (ng/ml)	% Plasma lactone	CSF total (ng/ml)	CSF lactone (ng/ml)	CSF/plasma ratio (%)
0.25	1.02 (3)	0.42 (1)	34.3	ND	ND	
0.5	2.48 (3)	1.07 (3)	43.1	0.45	ND	17.8
0.75	2.74 (4)	0.54 (4)	23.2	0.76	ND	21.8
1.0	4.15 (5)	1.36 (5)	34.8	1.09	0.5 (1) ND (3)	28.0

ND Not detectable

Discussion

Chemotherapy treatment of central nervous system neoplasms has been felt to be of limited potential due to the presence of the blood–brain barrier which impedes the ability of chemotherapeutic agents to cross over into the central nervous system in effective concentrations. However, reports of tissue levels of drugs, and observations of responsive disease in both primary and metastatic central nervous system tumors in patients treated with chemo- or hormonal therapy, suggest that the blood–brain barrier may be only partially intact in affected areas [18–22]. Furthermore, measurable CSF levels of chemotherapeutic agents have been reported for many agents [4, 23–25]. It is therefore important to further investigate the role of systemic agents in the treatment of CNS malignancies.

High-dose tamoxifen has been shown to be active in primary CNS malignancies [20, 26–28]. The presumed mechanism of action includes protein kinase C inhibition which is important in growth regulation of glial cells in vitro. Reduced levels of intracellular protein kinase C in cell cultures treated with tamoxifen has also been shown to enhance cisplatin cytotoxicity. Treatment with single agent tamoxifen at doses of 160–200 mg/d resulted in tumor reduction or stabilization in 4/11 patients reported by Couldwell et al. 1993.

Carboplatin and topotecan are also active agents in primary central nervous system tumors [29] and in solid tumors which commonly metastasize to the brain including breast, ovarian [30], and lung cancer [9, 31, 32]. Multani [32] administered topotecan on a daily $\times 5$ schedule to a patient with leptomeningeal metastasis from ovarian cancer and reported the clearance of malignant cells from the CSF. Further testing of the combination reported in this manuscript could be considered to determine its efficacy in this condition. Additional phase I and II studies have been reported in which responses to single agent topotecan have been observed in primary central nervous system tumors [33]. Our measured concentrations in vivo are lower than previously reported in vitro IC₅₀ values [34], although IC₅₀ measurements for topotecan are known to be cell line and time dependent [35]. In our study, we observed two minor

responses in relapsed glioma patients and two objective CNS responses in patients with metastatic carcinoma suggesting that this combination is active.

Primate models have been used to assess the pharmacokinetics of intravenously administered topotecan, and have demonstrated CNS penetration [36, 37]. Baker et al. 1996 treated patients with 24- and 72-hour continuous infusions, and have reported median penetrations of 29 and 42% of plasma levels, respectively. We determined a CSF/Plasma² ratio of 21.8% confirming these findings.

In vitro, platinum agents and topotecan have been administered in combination and have been shown to be synergistic [38, 39]. In vivo data suggests that the sequence of platinum followed by topotecan results in greater toxicity than the reverse sequence but with equal cytotoxic effect [40]. We designed this regimen to take advantage of the known single agent activity of the three agents and to exploit the known synergy. The toxicity of the combination observed in this trial is primarily myelosuppression. Two episodes of venous thrombosis in patients with lung cancer were also observed. It is unclear if these are related to the administration of high-dose tamoxifen or to the known propensity of patients with lung carcinomas to develop venous thrombosis.

Recent literature attests to the need to consider whether the co-administration of P-450 enzyme-inducing anti-epileptic drugs (EIAED), which interact with some chemotherapeutic agents, alters their pharmacokinetics and leads to an inaccurate determination of the recommended phase II dose [41, 42]. The data presented in our study suggests that the MTD is unchanged by the presence or absence of concurrently administered EIAED. All six patients on dose level 3 (our suggested phase 2 dose) including one patient treated without enzyme-inducing agents were observed to tolerate these doses without myelosuppression. Four of five patients treated at dose level 4 were observed to have dose-limiting thrombocytopenia or neutropenia, including one patient receiving carbamazepine. These data suggest that the recommended phase II doses are acceptable without the need to adjust for the presence or absence of enzyme-inducers. Furthermore, two of the responding patients (both on the recommended phase II dose) were receiving phenytoin during their participation on this study.

We have determined that the recommended phase II dose of topotecan when administered in combination with carboplatin and tamoxifen is 0.75 mg/m²/d for 72 h. The dose-limiting toxicity included myelosuppression and the development of a deep venous thrombosis in one patient, but the regimen was otherwise well tolerated. Minor responses were noted in patients with high-grade glial tumors, and objective partial responses were seen in two patients with metastatic lung cancer. CSF penetration was documented through topotecan assays, both total and lactone, in the cerebrospinal fluid. The concentration was 22% of the peak systemic level at the recommended phase 2 dose. Our data suggest that this combination may have activity in central nervous system tumors.

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Conflict of interest statement None.

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