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Clinical–patient studies

Salvage chemotherapy With CPT-11 for recurrent meningioma

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Summary

Background: A prospective Phase II study of irinotecan (CPT-11) in adult patients with recurrent surgery and radiotherapy-refractory WHO Grade I meningioma.

Methods: Sixteen patients (5 men; 11 women) ages 48–70 years (median 62.5), with recurrent meningioma were treated. All patients had previously been treated with surgery (complete in 4; partial in 9; biopsy in 3) and involved-field radiotherapy (median dose 54 Gy; 12 following first surgery and 4 following second surgery). Additionally, eight patients underwent re-operation (complete in 2; partial in 6) and eight patients were treated with salvage stereotactic radiosurgery. No patient was treated with prior chemotherapy. CPT-11 was administered intravenously every 3 weeks (350 mg/m^2/day in patients on non-enzyme inducing anticonvulsants [NEIAED]; 600 mg/m^2/day in patients on enzyme-inducing anticonvulsants [EIAED]) for 9 weeks (operationally defined as a single cycle). Neurological and neuroradiographic evaluation were performed every 10 weeks.

Results: All patients were evaluable. A median of two cycles of CPT-11 (range 1–4) was administered. CPT-11 related-toxicity (≥grade 3) included diarrhea (6 occurrences, 19% all cycles administered), granulocytopenia (6, 19%), leukopenia (5, 16%), thrombocytopenia (3, 10%) and anemia (3, 10%). Four patients required transfusion (3 RBC and 1 platelet). One patient developed neutropenic fever without bacteriologic confirmation. No treatment-related deaths occurred. No patient demonstrated a neuroradiographic complete or partial response (PR), 13 patients (81%) demonstrated stable disease but disease progressed after 2 cycles of CPT-11, and 3 patients (19%) had progressive disease (PD) following a single cycle of CPT-11. Time to tumor progression ranged from 2.5 to 5.0 months (median 5.0 months). Survival ranged from 4 to months (median 7.5 months).

Conclusions: The primary objective was to estimate the 6-month progression-free survival (PFS) after study entry. As no patient demonstrated PFS at 6-months, the study was stopped prematurely as specified by study design. Using CPT-11 in this moderately toxic dose schedule failed to demonstrate efficacy in this cohort of adult patients with recurrent surgery and radiotherapy-refractory meningioma.

Introduction

Meningiomas are extra-axial brain tumors of middle to late adult life and have a female predominance. Overall, 90% of meningiomas are benign, 6–8% atypical and 2–3% are malignant [1,2]. Most patients diagnosed with a meningioma decide to have it removed surgically and are advised to do so based on their neurological symptoms [3–8]. Complete surgical resection may be curative. For incompletely resected or recurrent tumors not previously irradiated, radiotherapy is administered [2,7–13]. Radiotherapy may be administered as either conventional external beam irradiation or stereotactically. Stereotactic radiotherapy (SRT) either as LINAC, gamma knife or cyberknife radiosurgery is increasingly utilized. Advocates of SRT have suggested this therapy in lieu of surgery particularly in poor surgical risk patients, patients with meningiomas in eloquent or surgically inaccessible locations and in patients of advanced age [9–13]. When the meningioma is unresectable or all other treatments (surgery, radiotherapy) have failed, immuno-chemotherapy may be considered [14]. Hydroxyurea, alpha interferon, tamoxifen, temozolomide and mifepristone (RU-486) have had limited success in patients with recurrent meningiomas whereas cyclophosphamide, adriamycin and vincristine (CAV), ifosphamide/mesna or adriamycin/dacarbazine (DTIC) have been administered to patients with aggressive or malignant meningiomas [14–25].

Irinotecan (CPT-11) has been increasingly used for a variety of glial brain tumors based on CPT-11 ease of use and modest efficacy. In addition, a single report suggests *in vitro* activity of CPT-11 against meningiomas [26]. This prospective Phase II trial was undertaken to evaluate efficacy of CPT-11 in patients with recurrent WHO Grade I meningiomas having previously failed surgery and radiotherapy.

Patients and methods

The study was performed at the University of Southern California, Norris Comprehensive Cancer Center and Hospital. The study was activated in November 1999

and closed in October 2004. Approval of the protocol and informed consent by the university human investigation committee was obtained. Informed consent was obtained from each subject.

Eligibility criteria

Patients must have had a histologically proven WHO Grade I meningioma that was recurrent. Patients must have progressed following definitive radiotherapy. At least 6 months must have elapsed since the last radiotherapy and patients must have recovered from the adverse effects of prior therapy. Patients could not have received prior chemotherapy. Patients must have radiographically measurable intracranial disease wherein recurrent tumor is bi-dimensionally measurable (at least 1×1 cm) by cranial contrast-enhanced magnetic resonance imaging (MRI). Histological confirmation of tumor recurrence was not required for entry into study. Pregnant or lactating women were not permitted to participate. Patients of child bearing potential were required to implement adequate contraceptive measures during participation in this study. Patients must have had a Karnofsky performance status of greater than or equal to 60 and a life expectancy greater than 3 months.

Adequate hematologic, renal and hepatic functions were required and were defined by the following: absolute granulocyte count >1500/dl or white blood cell count >4000/dl, platelet count $>100{,}000$/dl, total bilirubin level <1.8 mg/dl, transaminase level <4 times the upper limit of normal, and creatinine concentration <1.8 mg/dl (or creatinine clearance greater than or equal to 60 ml/m^2/1.73).

All patients were aware of the neoplastic nature of their disease and willingly consented to participate after being informed of the procedures to be used, experimental nature of the therapy, alternatives, potential benefits, side effects, risk, and discomforts. Patients with carcinomatous meningitis were not eligible. No serious concurrent medical illnesses or active infection could be present that would jeopardize the ability of the patient to receive CPT-11 therapy. Patients could not have an active concomitant malignancy except skin cancer (squamous cell or basal cell). Patients could range in age from 20 to 80 years.

Imaging

Cranial MR examinations were performed on a 1.5-Tesla super-conducting magnet (Signa, General Electric). Using a spin-echo pulse sequence, axial T_2-weighted (T_2W; TR 3000 ms/TE 80 ms), proton density-weighted (PDW; TR 3000 ms/TE 30 ms) images were initially acquired. Subsequently, both sagittal axial and coronal T_1-weighted (T_1W; TR 600 ms/TE 25 ms) images were acquired. Slice thickness was 5-mm, with a 2.5-mm interval between successive slices in all instances; a 256×256 matrix was used. After intravenous administration of 0.1 mmol/kg of gadolinium-pentetic acid dimegulmine (Berlex Laboratories, Cedar Knolls, New Jersey), coronal, axial and sagittal T_1W sequences (TR 600 ms/TE 25 ms) were obtained. All post-contrast images were obtained within 30 min of gadolinium infusion. A panel of two radiologists independently reviewed cranial contrast-enhanced MR images.

Drug schedule

Irinotecan (CPT-11: Pharmacia Pharmaceuticals, Kenilworth NJ) was administered to all patients at a dose of 350 mg/m^2 (in patients on either no AED or NEIAED) or 600 mg/m^2 (in patients on EIAED) intravenous every 3 weeks. A cycle of therapy was defined as 3 CPT-11 treatments (9 weeks). Treatment cycles were repeated every 9 weeks provided that all hematologic toxicity from the previous cycle had resolved to grade 2 or less, and all non-hematologic toxicity had resolved to grade 1 or less. If recovery had not occurred by day 70, the subsequent cycle of CPT-11 was delayed until these criteria were met. No dose escalations were allowed. Dose reduction for toxicity was allowed in 25-mg/m^2/day reduction increments. Only two dose reductions were permitted, and patients having grade 3 toxicity of any type after two dose reductions were removed from study. All toxicities including hematologic due to CPT-11 therapy were rated according to the NIH Common Toxicity Criteria (version 3.0). Patients were pretreated with oral antiemetics and antidiarrheals before each CPT-11 dose and as needed symptomatically.

Concurrent dexamethasone was permitted for control of neurologic signs and symptoms. Oral dexamethasone was used concurrently in 12 patients and was increased in 6 patients with clinical disease progression. Dexamethasone dose remained stable in 6 patients as patient clinical status permitted.

Method of evaluation

Blood counts were obtained weekly, neurologic examination was performed every 9 weeks, and contrast-enhanced cranial MR was performed every 9 weeks. A single cycle of CPT-11 was operationally defined as 9 weeks (3 CPT-11 administrations, each separated by 3 weeks).

Neuroradiographic response criteria were as follows [27]. Complete response (CR) was defined as the disappearance of all enhancing or non-enhancing tumor on consecutive MR scans at least 2 months apart, with the patient off corticosteroids, and neurologically stable or improved. Partial response (PR) was defined as a $>50\%$ reduction in the size of tumor on consecutive MR scans at least 2 months apart, with the corticosteroid dose stable or decreased and the patient neurologically stable or improved. Progressive disease (PD) was defined as a greater than 25% increase in the size of tumor or any new tumor on MR scans, or the patient neurologically worse with a stable or increased corticosteroid dose. Stable disease (SD) was defined as all other situations.

In patients with SD, PR or CR, one additional cycle of CPT-11 was to be administered, following which patients were assessed again as described. Patients were continued on CPT-11 therapy until documentation of PD at which time patients were removed from study and

were either monitored expectantly or offered alternative therapy (patients with PD).

Progression-free survival (PFS) and overall survival (OS) were defined as the time from the first day of treatment until progression or death. Patients were removed from study if there was PD, development of unacceptable toxicity, an unacceptable status quo or patient refusal, or noncompliance with protocol requirements.

Statistical considerations

This was a phase II study to investigate the efficacy of CPT-11 in the treatment of recurrent meningioma. The primary objective of the statistical analysis was to estimate the 6-month PFS after study entry. Since recurrent meningiomas are known to exhibit prolonged periods of stable disease, classical response was not considered an acceptable endpoint for assessment of treatment efficacy. Therefore, the primary endpoint for statistical analysis is the 6-month PFS status; as such, a patient who was alive and free of progression at 6 months was considered to have a favorable outcome. Secondary objectives include response rate, median survival, median time to progression, and the rate of toxicity, especially those that result in a significant modification or cessation of CPT-11 therapy. There was no stratification in this study. It has previously been demonstrated that patients on anticonvulsant drugs (AED) depending upon hepatic enzyme induction who receive CPT-11 have different tumor exposures to CPT-11. Therefore CPT-11 dose modifications were made for whether or not hepatic enzyme inducing AED (EIAED and NEI-AED) were utilized. A Simon minimax two-stage design was used: if the chance of remaining alive and free of progression at 6 months were 15% or less, then there would be little interest in further studying CPT-11 on this schedule, and if there was a 40% or greater chance that a patient would remain alive and free of progression at 6 months, then there consideration would be given to studying CPT-11 further, provided safety and other endpoints were also favorable. With this design, in the first stage, 16 patients were entered. If two or fewer patients demonstrated PFS of 6 months or more, the study would be stopped. If three or more patients demonstrated 6+-month PFS, then an additional 11 patients would be enrolled and treated. If 6 or fewer of the 27 patients were alive and free of progression at 6 months, then there would be little interest in studying this schedule of CPT-11 further. With this design, there was a 95% chance that we would recommend CPT-11 for further study if the true 6-month PFS were 40% or greater (power) and there was a 10% chance of deciding to study CPT-11 further if the true chance of 6-month of PFS were 15% or less (type 1 error). In patients who discontinued CPT-11 therapy because of toxicity, response was the best-recorded response through the cessation of CPT-11.

Results

Sixteen patients with surgery and radiotherapy refractory recurrent meningioma were entered on study. All patients were evaluable for both response and toxicity.

The median age was 60.5 years (range, 47–73 years). Twelve subjects were female and 9 were male. Eleven subjects were Caucasian, 3 Asian, 3 Hispanic and one African-American. Karnofsky performance status ranged from 60–100 with a median of 80.

Prior treatment is listed in Table 1. All patients had prior surgery (gross total resection in 8, subtotal resection in 6 and biopsy in 2) in which pathology confirmed a WHO Grade I meningioma. Eight patients (50%)

Table 1. Recurrent meningioma: salvage therapy with CPT-11

Patient	Gender/Age (Years)	Adjuvant therapy			Salvage therapy		CPT-11 Salvage therapy		
		Tumor location	Surgery	Radiation (Gray)	Surgery	Radiotherapy	# Cycles	Response/Duration in months	Survival in months
1	F/59	L Frontal	GTR		STR	54	1	PD/2.25	7
2	M/61	R Temporal	GTR		GTR	54	2	SD/4.5	8
3	F/60	L Cavernous sinus	Bx	54		16[a]	2	SD/4.5	6
4	F/68	R Frontal	STR	54		18[a]	2	SD/4.5	8
5	F/54	R Tentorium	GTR		GTR	54	2	SD/4.5	7
6	F/50	L Frontal	GTR		GTR	54	4	PR/10.5	13
7	F/61	L Parietal	STR	54		18[a]	2	SD/4.5	8
8	M/59	L Occipital	GTR		GTR	54	3	SD/6.0	9
9	F/68	L Temporal	GTR			54	2	SD/4.5	6
10	M/73	R Parietal	GTR		STR	54	2	SD/4.5	7
11	F/68	L Frontal	STR	54			1	SD/2.25	5
12	F/54	L Parietal	Bx	54		24[a]	1	PD/2.25	6
13	F/55	L Frontal	STR	54		18[a]	2	SD/4.5	8
14	F/66	L Tentorium	STR	54	STR		2	SD/4.5	8
15	M/66	R Cavernous sinus	Bx	54		18[a]	2	SD/4.5	7
16	F/47	L Frontal	GTR		GTR	54	1	PD/2.25	5

[a]Gamma knife radiotherapy.

M – Male; F – Female; R – Right; L – Left; GTR – Gross total resection; STR – Subtotal resection; Bx – Biopsy – PD; Progressive disease; SD – Stable disease.

underwent a second surgery (gross total in 5 and subtotal in 3) in which pathology remained a WHO Grade I meningioma. All patients received conventionally fractionated external beam radiotherapy (total dose 54 Gy), 8 following first surgery and 8 following second surgery. In addition, six patients (38%) were treated with gamma knife (median maximal dose 18 Gy, range 16–24 Gy) following disease recurrence. All patients experienced treatment failure with prior radiotherapy. All patients were chemotherapy naïve.

Response

Of 16 patients assessable for response (Table 1), there were 13 patients with stable disease following the first cycle of CPT-11 and 3 patients with PD. Ten patients with initially stable disease after first cycle of CPT-11 progressed following the second cycle of CPT-11. Two patients demonstrated either a PR (one patient) or stable disease pattern (one patient) after second cycle of CPT-11 and proceeded to a third cycle. Of these two patients, one progressed after three cycles and one after four cycles of CPT-11.

Survival

There were 16 eligible patients with recurrent meningioma analyzed by intent to treat (Figure 1). All patients have died of disease progression with a median OS of 7 months (range, 5–13 months, 95% confidence interval between 7 and 8 months). The overall PFS was 6% (one patient) at 6 months. Median time to tumor progression was 4.5 months (range, 2.25–10.5 months). Regarding the primary end point of the study, PFS at 6 months, the results failed to achieve our 25% threshold for success.

Treatment intensity

The median number of 9-week cycles was two (range, 1–4). All patients (100%) received at least one cycle of therapy and 13 (81%) received a second cycle of therapy. No patient was noncompliant with therapy. All patients went off of study as a result of PD with documented radiographic disease progression.

Toxicity

Toxicity was recorded for all grades for all patients using the NCI common toxicity criteria (version 3.0). Table 2 lists all grades 3 or higher toxicities observed with each figure representing the highest grade of toxicity attained, per patient, per cycle for all patients. In a total of 31 cycles, there were 30 (97%) grade 3 toxicities and 3 (11%) grade 4 toxicities. The most common grade 3 or 4 toxicities were diarrhea (6, 19% all cycles), granulocytopenia (6, 19%), leukopenia (5, 16%), and thrombocytopenia (3, 16%). Four patients required transfusion (3 RBC and 1 platelet). One patient developed neutropenic fever without bacteriologic confirmation of source. No treatment-related deaths occurred. No patients went off study because of toxicity, and no deaths were attributed to the drug regimen. No delay in therapy occurred nor was a dose reduction required as a consequence of toxicity.

Discussion

The management of recurrent meningioma has traditionally utilized re-operation or radiotherapy with stereotactic radiosurgery increasingly utilized. However there exists a subset of patients with recurrent meningioma desirous of further treatment in whom both surgical and radiotherapy options have been exhausted. It is in these patients that chemo-hormonal therapy may be considered. Several small studies have suggested that chemo-hormonal therapy may have some efficacy in patients with recurrent meningiomas however these studies unlike the present included patients who had not been treated with radiotherapy, a modality of therapy with established efficacy and frequent durable responses.

Both epidemiological and biochemical evidence (70% of meningiomas are progesterone receptor positive and 30% are estrogen receptor positive) has suggested meningioma growth may be hormone dependent [2]. As such a variety of hormonal therapies have been utilized

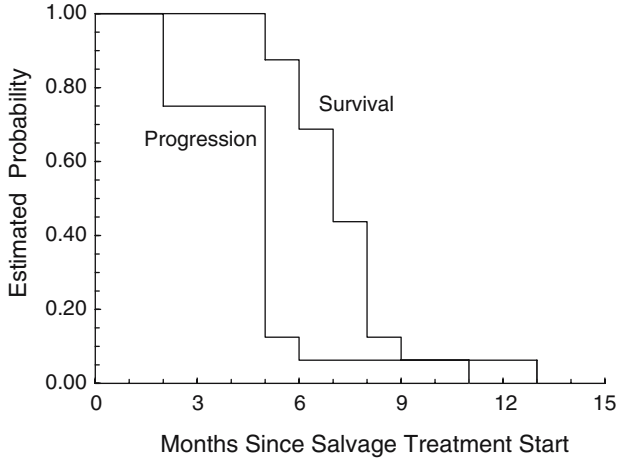

Figure 1. Overall survival and time to progression among 16 patients with recurrent meningioma treated with CPT-11.

Table 2. CPT-11 in recurrent meningioma: toxicity

Toxicity	Grade 3	Grade 4	Total
Anemia	2	1	3
Constipation	1	0	1
Diarrhea	5	1	6
Fatigue	1	0	1
Granulocytopenia	5	1	6
Headache	1	0	1
Infection, neutropenia	1	0	1
Leukopenia	5	0	5
Nausea	2	0	2
Seizures	2	0	2
Thrombocytopenia	3	0	3
Thrombophelbitis	1	0	1
Vomiting	1	0	1
Totals	30	3	33

in the treatment of recurrent benign meningiomas not otherwise treatable by surgery or radiotherapy. The oral progesterone agonist megestrol acetate (megace) was used in a small trial of nine patients with no observed response [15]. Subsequently, in a trial of 14 patients, the progesterone antagonist mifepristone (RU-486) was utilized [16]. Five objective minor responses were seen. In a subsequent European study by Lamberts, 10 patients were treated with RU-486 and minor responses were seen in 3 patients and 4 patients had stable disease [17]. These preliminary results prompted a Southwest Oncology Group Phase 3 trial of mifepristone versus placebo in 193 patients of whom 160 were evaluable [18]. No difference was seen between the studies arms (PFS in the RU-486 arm was 10 months; 12 months in the placebo arm). In addition, the SWOG reported on a Phase 2 trial of oral tamoxifen, an estrogen receptor antagonist, in 21 patients [14]. One patient achieved a PR, two patients had a minor response and six patients had stable disease for >6 months.

Recombinant alpha interferon has been found to inhibit the growth of cultured human meningioma cell lines *in vitro* [19–21]. Three small reports, two in abstract form, have been published. In the largest report, six patients with recurrent unresectable and previously irradiated meningiomas were treated. One patient had an objective response and four patients had stable disease for >6 months.

Schrell demonstrated *in vitro* that hydroxyurea, an oral chemotherapy with a variety of antitumoral effects, was a potent inhibitor of cultured meningioma cells by inducing apoptosis [22]. A subsequent trial by this group in 4 patients and another reported by Mason involving 16 patients suggested *in vivo* efficacy (no radiographic responses, 12 stable disease patterns for a median PFS of 122 weeks and 19% of patients manifested clinical improvement) [23]. In another study reported by Newton, 17 patients were treated amongst whom, 16 were evaluable for response [24]. Fourteen responded with stable disease for a median time to tumor progression of 80 weeks. However none of these patients manifested a radiographic response nor did any patient improve clinically.

Multi-drug chemotherapy trials for recurrent meningiomas whether aggressive, malignant or refractory to surgery and radiotherapy are scant [14,25]. The best-documented chemotherapy regimen (CAV) has been used primarily in an adjuvant setting for the treatment of malignant meningiomas. Other published regimens do not report response rates, length of response or toxicity data and therefore should be regarded as investigational [14].

The present study used CPT-11, an intravenous agent with modest toxicity and known activity in a variety of primary glial tumors for recurrent meningiomas progressing despite prior surgery and radiotherapy. This study differs somewhat from prior chemotherapy trials of recurrent meningioma mentioned above in that all patients had evidence of PD despite previous surgery (50% of patients underwent a second resection) and radiotherapy (all patients received prior external beam radiotherapy and 35% were treated in addition with SRT). Though only 50% of patients had reconfirmation of initial pathology, it seems reasonable to assume that the patients in this series are representative of patients with treatment-refractory recurrent meningiomas. A variety of surgical series have demonstrated the lethality of meningioma notwithstanding surgical resection with or without radiotherapy. Therefore we believe these patients are representative of recurrent meningioma patients seen in medical neuro-oncology clinic. The schedule of CPT-11 utilized is one of two commonly used however differences with respect to tumor response between weekly vs. every 3 weeks schedules of CPT-11 administration appear trivial. This regimen has been utilized in the treatment of recurrent glioblastoma multiforme however in that study, no clear benefit was observed with respect to either response or survival when compared to the more traditional 5-day drug schedule [28]. In addition this regimen (42 continuous days of CPT-11) has been used in an adjuvant setting (given concurrently with radiotherapy) for the treatment of glioblastoma and is being evaluated by a randomized phase III EORTC trial [29]. Toxicity was increased using this regimen as compared to the standard 5-day CPT-11 schedule however no patient required a CPT-11 dose reduction, delay in therapy, transfusion or treatment of neutropenic fever. This suggests that this regimen may be used with only modest toxicity not otherwise affecting treatment. Notwithstanding these presumed pharmacological benefits, only a single patient demonstrated PFS at 6-months, the primary study objective. As a consequence the study was terminated following enrollment of the first 16 patients. Based on the results of this study, CPT-11 does not appear to have activity against recurrent meningiomas (and perhaps by extrapolation aggressive and malignant meningiomas) suggesting a need for further phase I/II chemotherapy trials for this common primary brain tumor.

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