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CLINICAL-PATIENT STUDIES

CPT-11 for recurrent temozolomide-refractory 1p19q co-deleted anaplastic oligodendroglioma

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Abstract *Objective* A Phase II study of CPT-11 in adults with recurrent, temozolomide (TMZ)-refractory, 1p19q co-deleted, anaplastic oligodendroglioma (AO) with a primary objective of determining 6-month progression free survival (PFS). *Background* There is no standard therapy for alkylator-resistant AO. *Methods* Twenty-two patients (11 men; 11 women) ages 26–65 (median 40), with radiographically recurrent AO were enrolled. All patients had previously been treated with surgery, involved-field radiotherapy, and adjuvant chemotherapy (TMZ in 15; BCNU in 6). Fifteen patients were treated at first recurrence with an alternative chemotherapy. 13 patients underwent repeat surgery. All patients were treated at either first or second recurrence with CPT-11 administered intravenously once every 3 weeks. Neurological and neuroradiographic evaluations were performed every 8–9 weeks. *Results* All patients were evaluable for toxicity and response. A total of 141 cycles of CPT-11 (median 3 cycles; range 3–18) were administered. CPT-11 related toxicity included diarrhea (14 patients; 4 grade 3), neutropenia (8; 4 grade 3), fatigue (12; 3 grade 3), and delayed nausea/vomiting (12; 3 grade 3). 5 patients (23%) demonstrated a partial radiographic response, 8 (36%) demonstrated stable disease and 9 (41%) had progressive disease following three cycles of CPT-11. Time to tumor progression ranged from 2 to 13.5 months (median: 4.5 months). Survival ranged from 3 to 21 months (median: 5.5 months). Six-month and 12-month PFS were 33% and 4.5% respectively. *Conclusions* CPT-11 demonstrated modest efficacy (similar to other salvage glioma regimens) with acceptable toxicity in this cohort of adults with recurrent, 1p19q co-deleted AO all of whom had failed prior TMZ chemotherapy.

Keywords CPT-11 · Recurrent anaplastic oligodendroglioma · Temozolomide refractory

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Introduction

The treatment of recurrent anaplastic oligodendroglioma (AO) like all high-grade gliomas (HGG) is problematic, as only partially effective therapeutic modalities are available and there is a lack of a standard therapy for recurrence. These therapies include cytotoxic chemotherapy, radioactive implants, stereotactic radiotherapies, targeted chemotherapy and re-operation [1–12]. Chemotherapy for recurrent HGG is of modest benefit, primarily because response to chemotherapy is of limited duration. In an analysis of eight institutional phase 2 studies of

chemotherapy for recurrent high-grade gliomas, Wong reported that the response rate in recurrent anaplastic astrocytoma was 14% and progression free survival at 6 months was 31% [13]. The most active second-line therapies include the nitrosoureas, temozolomide (TMZ), procarbazine, *cis*-retinoic acid, and platinum compounds [14–22]. CPT-11 is an alternative chemotherapy with purported activity in recurrent high-grade gliomas [23–30].

The primary objective of this three-institution prospective Phase II trial was to observe whether CPT-11 given every three weeks (600 mg/m^2/day for patients on enzyme inducing anticonvulsant drugs {EIAED} or 350 mg/m^2/day for patients on either no AED or non-enzyme inducing anticonvulsant drugs {NEIAED}) could significantly delay progression in patients with neuroradiographically recurrent 1p19q co-deleted anaplastic oligodendroglioma (AO) as determined by 6-month progression free survival (PFS-6). Twenty-two adult patients with recurrent supratentorial AO previously treated with surgery, radiotherapy and TMZ were entered into this study.

Patients and methods

The study was performed at the University of Southern California, Norris Comprehensive Cancer Center and Hospital; the University of Massachusetts; and the University of South Florida, H Lee Moffitt Cancer Center and Research Institute. The study was activated in January 2000 and closed in March 2007. Approval of the protocol and informed consent by the university human investigation committee was obtained. Informed consent was obtained from each subject.

Objectives and end points

The two primary objectives of this study included determination of efficacy and toxicity of CPT-11 in the treatment of patients with TMZ-refractory recurrent or progressive 1p19q co-deleted AO. The primary end point was progression free survival at months (6-month PFS). Secondary end points included overall survival, time to progression and response. Toxicity was evaluated in all eligible patients receiving at least one cycle of CPT-11.

Eligibility criteria

Patients were required to have a histologically proven 1p19q co-deleted anaplastic oligodendroglioma (AO) that was recurrent neuroradiographically. Patients must have progressed following definitive radiotherapy (RT) and temozolomide (TMZ) chemotherapy. Patients may have received no more than two salvage chemotherapy regimens. At least four weeks must have elapsed since the last dose of chemotherapy and patients must have recovered from the adverse effects of prior therapy. Patients could not have received prior CPT-11. Patients were required to have radiographically measurable intracranial disease wherein recurrent tumor was bi-dimensionally measurable (at least 1 cm $\times$ 1 cm) by cranial contrast-enhanced magnetic resonance imaging (MRI). Histological confirmation of tumor recurrence was not required for study entry. 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 greater than or equal to 60, a life expectancy greater than 3 months, and age $\geq$18 years. 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. Patients could not have an active concomitant malignancy except squamous or basal cell skin cancer.

Adequate hematologic, renal and hepatic functions were required and were defined by the following: absolute granulocyte count >1,500/dl or white blood cell count >4,000/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).

Drug schedule

CPT-11 (irinotecan; Pfizer Pharmaceuticals, Princeton, NJ) was administered to all patients at a dose of 350 mg/m^2 in patients on NEIAED or 600 mg/m^2 in patients on EIAED [25]. CPT-11 was administered intravenously over 120 min on a single day. Concurrent dexamethasone was permitted for control of neurologic signs and symptoms. Premedication included antiemetics (ondansetron, granisetron, or dolasetron), dexamethasone (20 mg) and atropine (0.5 mg), all administered intravenously. Pre-chemotherapy hydration utilized one half liter of normal saline given intravenously over 1 h. No post-hydration intravenous fluids were administered.

Post-chemotherapy medication included prochlorperazine for nausea or vomiting and loperamide for diarrhea. CPT-11 administration was repeated 3 weeks after the initial dose. A cycle of therapy was operationally defined as 21 days during which CPT-11 was administered on day 1. Treatment with CPT-11 was repeated every 21 days, counting from the day of CPT-11 administration, provided that all hematologic toxicity from the previous cycle had resolved to grade 2 or less, and all non-hematologic toxicity had recovered to either grade 1 or less. If recovery had not occurred by day 21, the subsequent cycle of CPT-11

was delayed until these criteria were met. All toxicities including hematologic due to CPT-11 therapy were rated according to the NIH Common Toxicity Criteria (version 3.0 after 2003).

No dose escalations were permitted. A 25% dose reduction was mandated in patients with grade 3 or greater toxicity. Only two dose reductions were allowed. Patients having grade 3 toxicity of any type after two dose reductions were removed from study as were patients delayed more than 2 weeks from next scheduled chemotherapy.

Method of evaluation

Blood counts were obtained weekly, neurologic examination was performed every 3 weeks, and contrast-enhanced cranial MR was performed every 9 weeks (after 3 cycles of CPT-11).

Neuroradiographic response criteria as defined by Macdonald et al were used [31]. Complete response (CR) was defined as the disappearance of all enhancing or non-enhancing tumor on consecutive CT or MR scans at least 1 month 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 CT or MR scans at least 1 month 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 CT or MR scans, or the patient neurologically worse with a stable or increased corticosteroid dose. Stable disease (SD) was defined as all other situations, and, as with CR and PR, required a confirmatory MR scan 1 month after documenting best response.

In patients with SD, PR or CR, 3 additional cycles of CPT-11 were 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 or offered alternative therapy.

Progression free survival (PFS) and overall survival (OS) were defined as the time from the first day of treatment with CPT-11 until progression (PFS) or death (OS). Patients were removed from study if there was progressive disease, development of unacceptable toxicity, patient refusal or noncompliance with protocol requirements.

Experimental design and statistical methods

The primary objective was to determine whether CPT-11 could significantly delay progression in patients with recurrent AO. Historical values were obtained from analysis of a database of 350 patients with recurrent high-grade glioma (125 anaplastic gliomas; AG) treated on consecutive prospective phase II trials, in which 6-month progression free survival (6-month PFS) was 31% for AG [13]. The authors recognize that this comparison is only partially relevant as the trials by Wong analyzed all AG including AO. Nonetheless, there are no other published data sets regarding outcome of recurrent AO. The hypothesis tested were H_0: $P \leq P0$ versus H_1: $P \geq P1$, where P is the probability of remaining alive and progression free at 6-months, with a Type I error, $\alpha \leq 0.05$ and a Type II error $\beta \leq 0.20$. For AO, $P0$ was set at 0.25 and $P1$ at 0.45, looking for an improvement of 0.20. The current study was designed to accrue 40 AO patients. For AO patients, success was defined as observing more than 18 of 40 patients alive and progression free at 6-months (yielding $\alpha = 0.03$ and $\beta = 0.21$). The associations of overall survival and PFS with patient's baseline characteristics were tested using logrank test [32]. The Pike estimate of relative risk based on the logrank test [33] was used to provide a quantitative summary of the data, with 95% confidence intervals [34, 35]. The median survival, time to progression and the associated 95% confidence intervals were computed. Kaplan-Meier plots [36–38] were constructed to display the estimated probabilities of overall survival and time to progression.

Results

Study population

Twenty-two patients (11 men; 11 women) ages 26–67 years (median 40), with recurrent 1p19q co-deleted (by FISH) AO (original pathology including FISH analysis reviewed and confirmed in all cases by the participating institutions) (Table 1) were treated with CPT-11. Although the study was designed to evaluate 40 patients, slow accrual, competing therapies and the low likelihood of accruing the projected cohort prematurely ended the study. Recurrent AO was defined by objective neuroradiographic progression (>25% increase in tumor size) as compared with prior baseline neuroradiographic images using the criteria reported by Macdonald [31]. All neuroradiography was locally reviewed by two neuroradiologists blinded to treatment and by the participating neuro-oncologist (MCC or MJG). All qualifying MRI scans demonstrating progressive disease were performed within 2 weeks of the first cycle of CPT-11. Thirteen patients (59%) underwent a re-operation (subtotal in all) in which repeat tumor histology was consistent with 1p19q co-deleted AO.

Patients presented at the time of tumor recurrence with the following signs and symptoms: increasing headache (n = 18), worsening seizures (n = 12), altered mental status (n = 6), progressive hemiparesis (n = 6), new onset

Table 1 Characteristics in patient study

Variables	Number patients	Percent
Total patients	22	100%
Age		
>40	8	36%
≤40	14	64%
Median (range)	38	(27–47)
Sex		
Male	11	50%
Female	11	50%
Location of tumor		
Frontal	12	57%
Temporal	6	29%
Parietal	5	24%
Occipital	2	10%
Multilobar	5	24%
Extent of initial surgery		
STR	8	36%
GTR	7	32%
Biopsy	7	32%
TMZ chemotherapy		
≤8 cycles	10	48%
>8 cycles	11	52%
Median (range)	8	(2–12[a])
Best response to TMZ chemotherapy		
Complete response	0	0%
Partial response	5	22%
Stable disease	16	73%
Progressive disease	1	5%
Re-operation at recurrence		
Yes	13	59%
GTR	2[b]	9%
STR	11[c]	50%
No	9	41%
Number of cycles of CPT-11		
≤3 cycles	11	50%
>3 cycles	11	50%
Median (range)	3	(3–18)
Best response to CPT-11 treatment		
Complete response	0	0%
Partial response	5	22%
Stable disease	8	36%
Progressive disease	9	42%

[a] Maximum cycles of treatment allowed are 12 cycles

[b] One patient underwent 2 complete resections at recurrence

[c] Four patients underwent 2 partial resections at recurrence

homonymous hemianopsia (n = 1), and gait ataxia (n = 1). Patient performance status using the Karnofsky scale ranged from 60 to 100 (median 80) at the time of documented tumor recurrence and initiation of CPT-11 therapy. Tumor locations were as follows: frontal (n = 8), temporal (n = 4), parietal (n = 4), occipital [1], and multilobar [5].

All patients had been treated initially with surgery in which a complete resection was accomplished in 7 (resection of all visible contrast-enhancing tumor confirmed by MRI in the immediate post-operative period), partial in 8 and biopsy only in 7 (Table 1). Thirteen patients (59%) underwent a second surgery and 5 (23%) a third surgery prior to study entry.

All patients had previously been treated with limited-field radiotherapy (adjuvant in 21; at time of first recurrence in 1) (Table 1) and in all, conventional fractionated radiotherapy was used in which 1.8–2.0 Gy was administered daily, with a median tumor dose of 60 Gy (range 54–60 Gy). No patients were treated with stereotactic radiotherapy.

All patients were treated with either TMZ [16] or BCNU (6: Carmustine 5; Gliadel 1) chemotherapy following radiotherapy (Table 1). TMZ was administered in the standard 5-day schedule (200 mg/m^2/day for 5 consecutive days administered every 28 days). The 6 patients treated initially with BCNU received TMZ at first recurrence as did one prior chemotherapy naïve patient. Patients received a median of 8.5 TMZ cycles (range 2–12 cycles). Five patients received one other chemotherapy (all PCV) and 2 patients received two other chemotherapies (in one Sorafenib followed by SDX (L-alanosine) and in another cyclophosphamide followed by carboplatin) following adjuvant TMZ and prior to initiating CPT-11. All patients began CPT-11 immediately following documentation of tumor progression after treatment with TMZ (except for the 7 patients mentioned above) as demonstrated by neuroradiographic progression (in all patients) or clinical disease progression (60% of patients). Eight patients began CPT-11 at first recurrence, 12 at second recurrence and 2 at third recurrence (median onset of CPT-11 following 2nd recurrence, range 1–3 recurrences). Median time to initiation of CPT-11 following initial surgery was 51.5 months with a range of 17–173 months. A total of 141 cycles of CPT-11 were administered. A minimum of three cycles of CPT-11 was administered to each patient with a median of 3 cycles (range 3–18). CPT-11 was administered at the prescribed dose in all patients. No other anti-glioma agents aside from dexamethasone were utilized during the study. Oral dexamethasone was used concurrently in 16 patients and was increased in 8 patients with clinical disease progression. Dexamethasone dose was decreased in 6 patients as patient clinical status permitted. Seven patients received another chemotherapy following progression on CPT-11 (4 hydroxyurea + imatinib, 3 carboplatin).

Toxicity

Toxicity was recorded for all grades for all patients by type using the NCI common toxicity criteria (version 3.0 after

Table 2 CPT-11 in recurrent anaplastic oligodendroglioma: toxicity

Toxicity	Grade 2	Grade 3	Grade 4	Grade 5	Total
Alopecia	3	0	0	0	3
Anemia	9	1	0	0	10
Constipation	4	0	0	0	4
Diarrhea	10	4	0	0	14
Fatigue	9	3	0	0	12
Granulocytopenia	4	4	0	0	8
Infection, without neutropenia	2	1	0	0	3
Leukopenia	8	1	0	0	9
Nausea	9	2	0	0	11
Thrombocytopenia	7	0	0	0	7
Thrombophlebitis	0	1	0	0	1
Vomiting	9	3	0	0	12
Totals	74	20	0	0	94

2003). Table 2 lists all Grade 2–5 toxicity observed with each figure representing the sum of the highest grade of toxicity attained, per toxicity, per cycle for all patients. A total of 141 treatment cycles were administered of which there were 21 (14%) grade 3 adverse events (AEs) and no grade 4 or 5 AEs. The most common grade 3 AEs were diarrhea (2.8%), granulocytopenia (2.8%), fatigue (2.1%), vomiting (2.1%), nausea (1.4%), anemia (0.7%), leukopenia (0.7%), neutropenia with infection (0.7%) and thrombophlebitis (0.7%). Two patients required transfusion with packed red blood cells. One patient developed febrile neutropenia however body fluid cultures were negative. No treatment-related death occurred.

Response

All patients were assessable for response and 21 patients for survival (Figs. 1 and 2). Following three cycles of CPT-11, 9 patients (41%) demonstrated progressive disease. Fourteen patients (40%) received six or greater cycles of therapy. At the conclusion of CPT-11, Karnofsky performance status ranged from 40 to 70 with a median of 60 in the entire study group. Survival in the entire cohort ranged from 3 to 21 months with a median of 5.5 [95% CI: 3.2–7.8] months. The probability of survival at 6 and 12 months was 33% and 4.5% ± 7%. Twenty one patients have died, and all deaths were directly attributable to the effects of progressive intracranial tumor.

No patient demonstrated a complete response, 5 patients (23%) demonstrated a neuroradiographic partial response [95% CI: 11%, 39%] and 8 patients (36%) demonstrated stable disease [95% CI: 25%, 57%]. In patients with a neuroradiographic response or stable disease (13 patients;

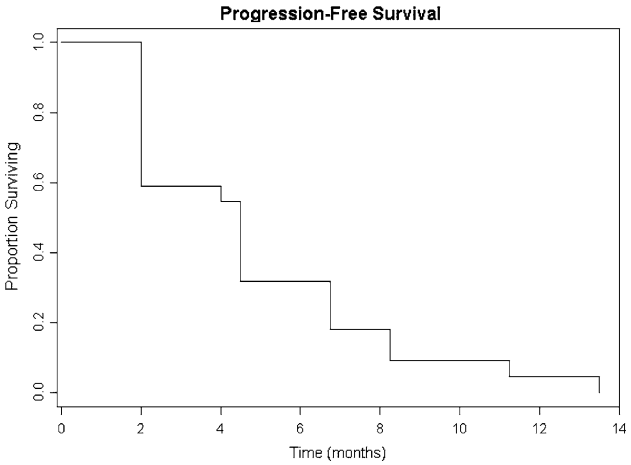

Fig. 1 Progression free survival following administration of CPT-11 for recurrent 1p19q co-deleted AO

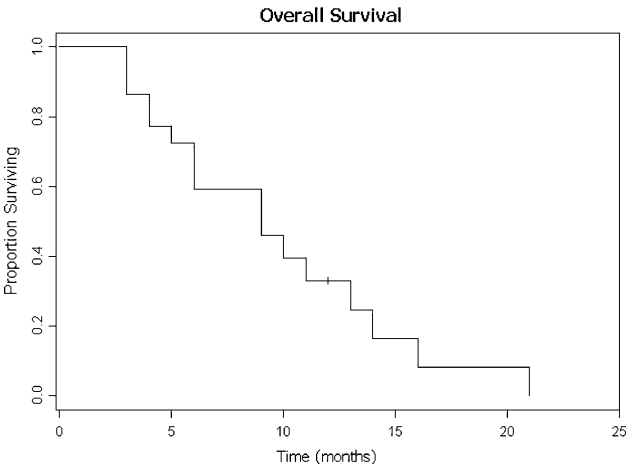

Fig. 2 Overall survival following administration of CPT-11 for recurrent 1p19q co-deleted AO

58%), median time to tumor progression was 6.75 months (range: 4–13.5 months) [95% CI: 5.2–8.3 months] and median survival was 9 months (range: 4–16 months) [95% CI: 6.8–11.2 months]. The overall probability of progression free survival at 6-months was 33% [95% CI: 16%, 44%] and at one year was 4.5% [95% CI: 0%, 16%]. Overall median time to tumor progression was 4.5 months (range: 2–13.5) [95% CI: 3.1–5.9 months]. Regarding the primary endpoint of the study (6-month PFS), the results failed to achieve the specified critical value: i.e. only 7, and not the required 9, patients experienced PFS of greater than 6 months (expected 45%; observed 33%) [13].

There was no association between response to CPT-11 and response to the prior regimen of TMZ, recognizing very few responses to TMZ were observed. No difference was seen in the pretreatment tumor volume in patients with either a CPT-11 partial response or stable disease as compared to

patients with progressive disease [37, 38]. Age ≤40 and frontal lobe tumor location were significantly associated with overall and progression-free survival ($P \leq 0.05$).

Discussion

Two recently reported cooperative group trials, one by the Radiation Therapy Oncology Group (RTOG) and the other by the European Organization for Research and Treatment of Cancer (EORTC), evaluated adjuvant chemotherapy in the treatment of AO/AOA (anaplastic oligoastrocytoma) [39, 40]. Both trials utilized PCV (procarbazine, CCNU, vincristine) although administration of PCV was both neoadjuvant and dose intense in the North American (RTOG) trial and adjuvant (standard dose and schedule) in the European trial (EORTC). In neither study was (neo)adjuvant PCV associated with improved survival. A benefit was seen with respect to progression free survival in the RTOG trial, but only in patients with 1p19q co-deleted AO. In addition, both trials demonstrated by molecular analysis that 25% (EORTC) to 50% (RTOG) of histologically defined AO/AOA contained the 1p19q co-deletion. This group of patients (1p19q co-deleted) had improved overall and progression free survival irrespective of treatment and constitutes a unique and identifiable tumor type. Partially or non-1p19q deleted AO/AOA behave like anaplastic astrocytomas with respect to outcome. Both cooperative group trials concluded that 1p19q co-deleted AO/AOA is a distinct tumor type separable from other anaplastic gliomas (AG) deserving of independent clinical trials. The studies also concluded that genotyping AO/AOA is not recommended outside of clinical trials as therapy does not differ from other anaplastic gliomas notwithstanding the nearly two-fold improved outcome in patients with 1p19q co-deleted AO/AOA.

In the recent meta-analysis by the Glioma Meta-analysis Trialists Group of 12 randomized trials, adjuvant chemotherapy improved 2-year survival by 6% in anaplastic gliomas (AG) (31% vs. 37%) [10, 11]. The meta-analysis suggests a modest benefit for the inclusion of chemotherapy in the adjuvant treatment of AG although the choice of adjuvant chemotherapy agent has evolved. The present study utilized adjuvant TMZ following RT as is common neuro-oncology practice and supported in part by the recent EORTC trial of adjuvant TMZ for glioblastoma demonstrating a survival benefit when compared to RT only controls (15 vs. 12 months) [41].

How best to manage recurrent AO remains ill-defined notwithstanding a variety of studies. Most studies however (and similar to the present study) are small Phase II non-randomized trials comparing outcome to historical controls. Only a minority of patients with recurrent AO (none in the present study notwithstanding nearly half underwent re-resection) are candidates for image-verified complete or near complete re-resection followed by Gliadel implantation. Therefore, the majority of patients, if desirous of further therapy, are offered chemotherapy. PCV has been used in TMZ refractory AO in an EORTC trial with response rates of 17% and 6-PFS of 25% [42]. By way of comparison, in the present study 50% of patients had, in addition to TMZ chemotherapy, been treated with a nitrosourea (BCNU, Gliadel or PCV) and consequently at time of recurrence, an alternative non-alkylator-based therapy was attractive. Carboplatin (with or without teniposide) has been used in several trials for recurrent AO with response rates of 9–13% and 35% 6-PFS [20, 21], results not dissimilar to the present study. Three other investigational treatments for recurrent HGG, intra-tumoral delivery of radiopharmaceutical toxins, antiangiogenic agents i.e. bevacizumab and molecularly targeted therapies such as small molecule inhibitors of receptor tyrosine kinases are presently under active study [43, 44]. How to adapt these treatments into the care of patients with recurrent AO outside of investigational trials is unclear.

The present study was directed at the 1p19q co-deleted AO population which had failed prior chemotherapy (TMZ in 100%; 50% nitrosoureas) and for whom further treatment appeared warranted. The study did not require histological proof of recurrent AO and the possibility of radiation necrosis as opposed to recurrent tumor is possible. This appears unlikely for the following reasons. No patient received stereotactic radiotherapy and the risk of radiation necrosis is <5% in patients treated with standard fractionated radiotherapy. Further, 15 patients (68%) underwent FDG-PET and 10 patients (45%) MR spectroscopy in which recurrent viable tumor was radiographically confirmed. Lastly, 13 patients (59%) underwent re-operation in whom histopathology was re-confirmed. Because this study did not require re-operation prior to enrollment, a proportion of patients assumed to have AO may have progressed to glioblastoma. Therefore the study may be evaluating both patients with AO and secondary glioblastoma.

CPT-11 appears attractive as prior single agent studies have suggested activity against HHG and in particular AA [23–30]. Furthermore, CPT-11 toxicity is manageable (approximately 25% grade 3 toxicity in the current study) and non-cumulative permitting administration without growth factor support. Of note, however, topoisomerase inhibitors like CPT-11, which have P450-mediated pharmacodynamic interactions with enzyme inducing anticonvulsant drugs, do require upward dose adjustment in patients receiving EIAEDs [25, 30].

In conclusion, CPT-11 used at this dose and in this schedule in patients with previously treated, TMZ refractory recurrent 1p19q co-deleted AO appears of modest

benefit (6-PFS of 33%), though not significantly different than other available chemotherapies for recurrent AG. Regarding the primary endpoint of the study (6-PFS), the results failed to exceed the 20% threshold for success, assuming a 20% improvement as compared to the database reported by Wong (anaplastic glioma: expected 45%; observed 33% [13].

References

1. The Medical Research Council brain tumor working party (2000) Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A Medical Research Council Trial. J Clin Oncol 19:509–518
2. Prados MD, Scott C, Curran WJ et al (1999) Procarbazine, lomustine, and vincristine (PCV) chemotherapy for anaplastic astrocytoma: a retrospective review of Radiation Therapy Oncology Group protocols comparing survival with carmustine or PCV adjuvant chemotherapy. J Clin Oncol 17:3389–3395
3. Westphal M, Hilt DC, Bortey E et al (2003) A phase 3 trial of local chemotherapy with biodegradable Carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 5(2):79–88
4. Grossman SA, O'Neill A, Grunnet M, Mehta M et al (2003) Phase III Study comparing three cycles of infusional carmustine and cisplatin followed by radiation therapy with radiation therapy and concurrent carmustine in patients with newly diagnosed supratentorial glioblastoma multiforme: Eastern Cooperative Oncology Group Trial 2394. J Clin Oncol 21:1485–1491
5. Prados MD, Levin V (2000) Biology and treatment of malignant glioma. Semin Oncol 27(Suppl 3):1–10
6. Gutin PH, Prados MD, Phillips TL et al (1991) External irradiation followed by an interstitial high activity iodine-125 implant "boost" in the initial treatment of malignant gliomas: NCOG Study 6G82-2. Int J Radiat Oncol Biol Phys 21:601
7. Loeffler JS, Alexander E, Shea WM et al (1992) Radiosurgery as part of the initial management of patients with malignant gliomas. J Clin Oncol 10(9):1379–1385
8. Prados MD, Gutin PH, Phillips TL et al (1992) Interstitial brachytherapy for newly diagnosed patients with malignant gliomas: the UCSF experience. Int J Radiat Oncol Biol Phys 24:593
9. Levin VA, Silver P, Hannigan J et al (1990) Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. Int J Radiat Oncol Biol Phys 18:321–324
10. Glioma Meta-analysis Trialists Group (2002) Chemotherapy in adult high-grade glioma: a systemic review and meta-analysis of individual patient data from 12 randomized trials. Lancet 359:1011–1018
11. Fine HA, Dear KB, Loeffler JS et al (1993) Meta-analysis of radiation therapy and without chemotherapy for malignant gliomas in adults. Cancer 71:2585–2597
12. Prados MD, Gutin PH, Phillips TL et al (1992) Highly Anaplastic Astrocytoma: a review of 357 patients treated between 1977 and 1989. Int J Radiat Oncol Biol Phys 23:3–8
13. Wong ET, Hess KR, Gleason MJ et al (1999) Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 17:2572–2578
14. Yung WKA, Mechtler L, Gleason MJ (1991) Intravenous carboplatin for recurrent malignant gliomas: a phase II study. J Clin Oncol 9:860
15. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M et al (1999) Multicenter Phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. J Clin Oncol 17:2762–2771
16. Longee DC, Friedman HS, Albright RE, Burger PC et al (1990) Treatment of patients with recurrent gliomas with cyclophosphamide and vincristine. J Neurosurg 72:583–588
17. Chamberlain MC, Tsao-Wei D (2004) Recurrent glioblastoma multiforme: salvage therapy with cyclophosphamide. Cancer 100:1213–1220
18. Brem H, Piantadosi S, Burger PC, Walker M, Selker R et al (1995) Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. Lancet 345:1008–1012
19. Jaeckle KA, Hess KR, Yung A et al (2003) Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study. J Clin Oncol 21:2305–2311
20. Soffieti R, Nobile M, Rida F et al (2004) Second-line treatment with carboplatin for recurrent or progressive oligodendroglial tumors after PCV chemotherapy: a phase II study. Cancer 15:807–813
21. Brandes AA, Basso U, Vastola F et al (2003) Carboplatin and teniposide as third-line chemotherapy in patients with recurrent oligodendroglioma or oligoastrocytoma: a phase II study. Ann Oncol 14:1727–1731
22. Triebels VH, Taphoorn MJ, Brandes AA et al (2004) Salvage PCV chemotherapy for temozolomide resistant oligodendrogliomas. Neurology 63:904–906
23. Batchelor TT, Gilbert MR, Supko JG et al (2004) Phase 2 study of weekly irinotecan in adults with recurrent malignant glioma: Final report of NABTT 97–11. Neuro Oncol 6:21–27
24. Buckner JC, Reid JM, Wright K et al (2003) Irinotecan in the treatment of glioma patients: current and future studies of the North Cancer Central treatment Group. Cancer 97:2352–2358
25. Chamberlain MC (2002) Salvage chemotherapy with CPT-11 for recurrent glioblastoma. J Neurooncol 56:183–188
26. Cloughesy TF, Filka E, Kuhn J et al (2003) Two studies evaluating irinotecan treatment for recurrent malignant glioma using an every 3-week regimen. Cancer 97:2381–2386
27. Friedman HS, Petros WP, Friedman AH et al (1999) Irinotecan therapy in adults with progressive malignant glioma. J Clin Oncol 17:1516–1525
28. Prados MD, Yung WKA, Jaeckle KA et al (2004) Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. Neuro Oncol 6:44–54
29. Prados MD, Lamborn K, Yung WKA et al (2006) A Phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. Neuro Oncol 8(2):189–193
30. Gilbert MR, Supko JG, Batchelor T et al (2003) A Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. Clin Cancer Res 9:2940–2949
31. Macdonald DR, Cascino TL, Schold SC et al (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277–1280
32. Miller RG Jr (1981) Survival Analysis. Wiley, New York, pp 114–118
33. Pike MC (1972) Contribution to the discussion on the paper by R. Peto and J. Peto, 'Asymptotically efficient rank invariant procedures'. J R Stat Soc Ser A 135:201–203
34. Berry G, Kitchin RM, Mock PA (1991) A comparison of two simple hazard ratio estimators based on the logrank test. Stat Med 10:749–755
35. Lawless JF (1982) Statistical models and methods for lifetime data. Wiley, New York, pp 345–354

36. Kaplan EL, Meier P (1958) Nonparametric estimation form incomplete observations. J Am Stat Assoc 53:457–481
37. Mantel N (1963) Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J Am Stat Assoc 58:690–700
38. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
39. van den Bent M, Brandes M, Frenay P et al (2005) Multicenter phase II study of imatinib mesylate in patients with recurrent anaplastic oligodendroglioma, anaplastic astrocytoma and low grade astrocytoma: an EORTC new drug development group and brain tumor group study. J Clin Oncol 23:118S (suppl: abstr 1528)
40. Cairncross G, Berkey B, Shaw E et al (2006) Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Oncology Group trial 9402. J Clin Oncol 24(18):2707–2714
41. Stupp R, Mason WP, Van Den Bent MJ et al (2004) Concomitant and adjuvant temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme. Conclusive results of a randomized phase III trial by the EORTC Brain & RT Groups and NCIC Clinical Trial Groups. J Clin Oncol 22:1s
42. Triebels VH, Taphoorn MJ, Brandes AA et al (2004) PCV chemotherapy for temozolomide resistant oligodendrogliomas. Neurology 63:904–906
43. Jaeckle KA, Ballman RD, Jenkins RB, Buckner JC (2006) Current strategies in treatment of oligodendroglioma: evolution of molecular signatures of response. J Clin Oncol 24(8):1246–1252
44. Vrendenburgh JJ, Desjardins A, Herndon JE 2nd et al (2007) Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13(4):1253–1259