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Phase II study of Gleevec® plus hydroxyurea in adults with progressive or recurrent low-grade glioma[1]

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Abstract

Background—We evaluated the efficacy of imatinib plus hydroxyurea in patients with progressive/recurrent low-grade glioma.

Methods—A total of 64 patients with recurrent/progressive low-grade glioma were enrolled in this single-center study that stratified patients into astrocytoma and oligodendroglioma cohorts. All patients received 500 mg of hydroxyurea twice a day. Imatinib was administered at 400 mg per day for patients not on EIAEDs and at 500 mg twice a day if on EIAEDs. The primary endpoint was progression-free survival at 12 months (PFS-12) and secondary endpoints were safety, median progression-free survival and radiographic response rate.

Results—Thirty-two patients were enrolled into each cohort. Eleven patients (17%) had prior radiotherapy and 24 (38%) had received prior chemotherapy. The median PFS and PFS-12 were 11 months and 39%, respectively. Outcome did not differ between the histologic cohorts. No patient achieved a radiographic response. The most common grade 3 or greater adverse events were neutropenia (11%), thrombocytopenia (3%) and diarrhea (3%).

Conclusions—Imatinib plus hydroxyurea was well tolerated among recurrent/progressive LGG patients but this regimen demonstrated negligible anti-tumor activity.

Keywords

imatinib; glioma; platelet derived growth factor; astrocytoma; oligodendroglioma

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Introduction

Low-grade gliomas (LGG), a histologically diverse group of progressively infiltrative primary CNS tumors including astrocytoma, oligodendroglioma and oligoastrocytoma, most commonly affect children and young to middle-aged adults. Although some historical reports have misnomered these tumors as benign, most likely due to growth rates as low as 3-5 mm/year,[1, 2] LGG can extensively infiltrate and cause progressive neurologic deficits, marked cognitive impairment and personality changes as well as recalcitrant seizures. In addition, many will eventually transform to high-grade histology.[3] Median survival for most LGG subtypes is 5-10 years.[4, 5]

Optimal therapy for LGG remains undefined. Maximum safe resection can palliate symptoms and improve prognosis,[6] but is not curative. Among newly diagnosed patients, post-surgical treatment is typically reserved for newly diagnosed patients with poor prognostic features including age over 40 years, poor performance status, tumors that are large or unresectable and non-oligodendroglial histology.[7, 8] For such patients, as well as those with progressive or recurrent tumors, radiotherapy has historically been regarded as appropriate initial therapy. Although radiotherapy successfully achieves tumor control in most cases, it is also associated with potential late sequellae including cognitive decline, neuro-endocrine dysfunction, radiation-induced necrosis, vasculopathy, cortical atrophy, secondary malignancy and diminished quality of life.[9-15] Due to these concerns, several chemotherapy options have been increasingly evaluated for LGG patients including PCV (procarbazine, carmustine and vincristine), carboplatin and temozolomide.[16-24] Chemotherapy strategies have demonstrated sufficient benefit to generate ongoing, randomized phase III studies.

A general therapeutic strategy of significant interest in the current oncology era is the inhibition of biologically relevant growth factors and cell signaling mediators. Platelet-derived growth factor receptor-α (PDGFR-α) expression is increased in some LGG.[25-29] In addition, PDGFR signaling is linked with several aspects of glioma biology including astrocytoma proliferation[30] and neural stem/progenitor cell transformation.[31]

In the current manuscript we describe the first evaluation of a targeted therapeutic in the treatment of LGG. Imatinib mesylate (Gleevec®, formerly STI-571), a selective receptor tyrosine kinase inhibitor of PDGF receptors, Bcr-Abl, c-KIT and c-fms, has established activity against both hematologic and solid organ cancers.[32] We performed a phase II study to evaluate the anti-tumor activity as well as safety of imatinib administered in combination with hydroxyurea, a ribonucleoside diphosphate reductase inhibitor, for patients with recurrent or progressive LGG.

Our results demonstrate that imatinib plus hydroxyurea is well tolerated but has negligible activity for patients with progressive or recurrent LGG.

Patients and Methods

Study design and treatment

We conducted an open-label, single center, phase II trial. The primary end point was 12-month progression-free survival (PFS) while secondary end points were overall survival (OS), median PFS, objective radiographic response rate and safety. Two patient cohorts, distinguished by tumor histology, were enrolled in parallel. Patients in cohort A had astrocytoma including the following histologic subtypes: fibrillary, gemistocytic, protoplasmic and pleomorphic xanthoastrocytoma. Patients in cohort B had oligodendroglioma or oligoastrocytoma. The dose of imatinib differed to account for the

effect of CYP3A-inducing anti-epileptic drugs (EIAEDs) on imatinib metabolism[33, 34]: patients not on EIAEDs received 400mg once a day, while those on EIAEDs received 500mg twice a day. All patients received 500 mg of hydroxyurea twice a day. Medically appropriate efforts were used to maintain study-specific EIAED exposure for all patients.

Patients were assessed every 8 weeks and remained on study unless they withdrew consent, developed tumor progression or unacceptable toxicity.

Patient eligibility

Adult patients (≥ 18 years of age) were required to have histologically confirmed LGG that was progressive or recurrent based on radiographic or clinical features, the latter defined as new/worsening neurologic deficits excluding seizures. Patients with intrinsic optic pathway tumors were eligible without histologic confirmation as long as one of the following criteria were met: progressive vision loss documented by ophthalmologic examination; worsened proptosis; ≥ 2 mm increase in optic nerve diameter; or increased tumor distribution within the optic tract or optic radiations on neuroimaging. Measurable disease was required for all patients. Satisfactory hematologic (hemoglobin ≥ 10 g/dL, absolute neutrophil count (ANC) > 1500 cells/L, platelets > 100,000 cells/L), biochemical (serum creatinine < 1.5 mg/dL, BUN < 25 mg/dL, AST and bilirubin < 1.5 × upper limit of normal) and performance status (Karnofsky ≥ 60%) parameters were also required. Patients were required to be at least 2 weeks from prior surgery and at least 4 weeks from prior radiation or chemotherapy. All patients provided informed consent.

Key exclusion criteria included: prior imatinib or PDGFR-directed therapy; prior progressive disease or grade ≥ 3 toxicity to hydroxyurea treatment; grade ≥ 2 peripheral edema; pulmonary, pericardial or peritoneal effusions of any grade; patients with an excessive risk of an intracranial hemorrhage, or who had evidence of hemorrhage on pre-treatment MRI unless it was stable and grade 1; and concurrent warfarin administration. There was no limit on the number of prior therapies or episodes of progressive disease.

Assessments

Disease status was assessed after every other cycle using a modified version of the Macdonald criteria,[35] to classify neurologic, corticosteroid and radiologic changes. In addition, the numeric cutoffs defined in the Macdonald criteria were also applied to the evaluation of the T2 or fluid attenuated inversion recovery (FLAIR) changes associated with the tumor to define response.

Safety assessments included weekly complete blood counts and monthly chemistry profiles. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Treatment Modifications

Initiation of each 28-day treatment cycle required an ANC ≥ 1000/mm^3, a platelet count of ≥ 100,000/mm^3, SGOT ≤ 2.5 times the upper institutional norm, and a creatinine ≤ 1.5 times the upper institutional norm. Dose modifications were implemented for unacceptable toxicity defined as grade 4 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 non-hematologic toxicity not attributable to underlying disease, concurrent medication or co-morbid event, or any toxicity requiring > two weeks to resolve to grade 1 or re-treatment criteria. Hydroxyurea was decreased to 500 mg once a day for the first episode of unacceptable hematologic toxicity. Thereafter additional episodes of unacceptable hematologic toxicity were treated with a decrease in total daily imatinib dosing of 100 mg/day for patients not on EIAEDs and 200 mg/day for patients on EIAEDs. For other

unacceptable toxicities, the hydroxyurea dose was decreased by 250 mg/day and the dose of imatinib was decreased by 100 mg/day for patients not on EIAEDs and 200 mg/day for patients on EIAEDs.

Statistical considerations

The primary endpoint of the current study was progression-free survival at 12 months (PFS-12) for each cohort. Secondary endpoints included time to progression, overall survival (OS), objective response rate as well as safety and tolerability. Given a 12-PFS rate of 76% (95% confidence interval [CI]: 63% to 92%) for recurrent/progressive LGG patients treated with the standard 5-day regimen of temozolomide,[20] a sample size goal of 32 patients per cohort was chosen to allow 90% power to differentiate between 12-PFS rates of 65% and 85% with a type I error rate of 0.082.

A “stopping rule” for unacceptable toxicity was incorporated for each stratum. Specifically, if 6 or more of the first 16 patients per stratum experienced unacceptable toxicity as defined above, further accrual would be suspended. In addition, if 9 or more of the total 32 patients experienced unacceptable toxicity, the treatment regimen would be considered to have an unacceptable toxicity profile. The type I and II error rates associated with this testing were 0.053 and 0.053, respectively.

Progression-free survival (PFS) and overall survival (OS) were measured from the cycle 1 start date and summarized using Kaplan-Meier estimator including 95% CIs.

Results

Patient characteristics

Sixty-four patients were enrolled between August 2005 and February 2008. Characteristics of patients at enrollment (Table 1) were comparable between the two cohorts except that oligodendroglioma patients were slightly older and were twice as long from the date of original diagnosis to study enrollment compared to the astrocytoma patients. In addition, a slightly higher percentage of oligodendroglioma patients had received prior chemotherapy. Approximately one-third of each cohort was on EIAEDs and approximately 17% of each cohort had received prior radiotherapy. A small subset of each cohort underwent either stereotactic biopsy or subtotal resection prior to enrollment and initiation of study therapy in order to confirm persistent LGG histology and demonstrate that these patients had not transformed to high-grade histology.

Toxicity

Seven-hundred and fifty-seven cycles of therapy were administered as of April 1, 2011. The adverse events seen in the study were as expected for this population and this class of therapy. They were mostly mild and transient and gave no indication of target organ toxicity. Table2 summarizes adverse events felt to be at least possibly attributable to the study regimen. Of note, the frequency and severity of adverse events did not differ between patient cohorts or between patients on and not on EIAEDs. Three patients (4.6%) were taken off study therapy due to toxicity including two patients with grade 4 neutropenia and one patient with asymptomatic, grade 1 CNS hemorrhage noted on surveillance MRI. Most adverse events were grade 2. Among grade 3 events, single patients experienced anemia, fatigue, infection and weight loss while diarrhea and thrombocytopenia affected two patients each and five patients experienced neutropenia. Grade 4 events were limited to neutropenia (n=2) and diarrhea (n=1), respectively. There were no grade 5 attributable adverse events. Dose modification was required in five patients including 2 astrocytoma patients and three oligodendroglioma patients; of note, all five of these patients were not on EIAEDs.

Outcome

Table 3 summarizes study outcome. As of April 1, 2011, median follow-up for all patients was 180 weeks and all patients have discontinued study therapy except for 1 oligodendroglioma patient who continues on treatment in cycle 51. Thirty-four patients (53%) elected to discontinue study therapy with stable disease while 27 patients (42%) came off study due to progressive disease. Three patients (5%) were taken off study therapy due to toxicity (discussed above).

Median PFS and PFS-12 for all patients were 43.5 weeks (95% CI: 33.0, 53.6) and 39.1% (95% CI: 27.2, 50.7). Of note, PFS did not differ between patients with astrocytoma or those with oligodendroglioma. Median OS was not reached for either study cohort. Best radiographic response was stable disease and none of the patients achieved a radiographic response. More than one episode of prior progression was associated with poorer PFS (p=0.005), while the presense of contrast enhancement had a borderline effect (p=0.07). In contrast, PFS was not related to age less than 40 years, KPS ≥ 90, maximum tumor unidimensional size greater than 6 centimeters, crossing the midline, oligodendroglioma histology or the concurrent administration of EIAEDs (Table 4).

Discussion

Low-grade glioma accounts for approximately 15% of adult primary central nervous system tumors. Large series have identified clinical factors associated with poor prognosis including age over 40 years, poor performance status, tumors that are large or unresectable and non-oligodendroglial histology.[7] More recently biologic factors have been linked with outcome including histology,[5] co-deletion of chromosomes 1p19q,[36] methylation of methylguanine methyltransferase,[19, 21] and IDH1/2 mutation.[37-39]

Beyond radiotherapy, optimal therapy for patients with poor prognostic factors or those with recurrent/progressive tumors have not been clearly identified. Several series have demonstrated that chemotherapy regimens such as PCV, and more recently including temozolomide, have activity in this setting.[17-21, 40-45]

The primary rationale for evaluating imatinib in this study is its inhibitory capacity against PDGFR. Low-grade gliomas, including both astrocytomas and oligodendrogliomas frequently express PDGFR while some of these tumors also express PDGF, implicating a potential autocrine and/or paracrine loop of dysregulated signaling.[26-28, 46] Several important findings also implicate PDGFR signaling in LGG physiology[47] including that exogenous PDGF induces astrocytoma proliferation[30] and that PDGFR activation has been linked with transformation of neural stem/progenitor cells into glial tumors[31, 48-51] In addition, PDGF dominant-negative mutants can revert the transformed phenotype of human astrocytoma cells.[52]

Imatinib has not been previously evaluated for patients with grade II glioma, however, preclinical in vitro assays have demonstrated activity against astrocytoma lines.[53] In addition, imatinib was anecdotally reported to elicit marked regression of a recurrent pilocytic astrocytoma (WHO grade I) in a pediatric patient.[54]

Hydroxyurea, a ribonucleoside diphosphate reductase inhibitor, exerts a cell-cycle specific effect during the S-phase of mitosis, thereby blocking DNA synthesis. Although hydroxyurea has is not known to have single-agent activity against malignant gliomas, it has been incorporated into several therapeutic regimens for primary CNS tumor patients.[55-59] Hydroxyurea exhibits rapid absorption from the gastrointestinal tract following oral dosing and readily crosses the blood-brain barrier. In the current study regimen for LGG patients,

we hypothesized that the cytotoxicity of protracted hydroxyurea dosing may augment the anti-PDGFR activity of imatinib yielding enhanced anti-tumor activity than could be achieved by either agent alone. Of note, modest activity of imatinib plus hydroxyurea was initially observed among recurrent high-grade glioma patients;[33, 60, 61] however, these results were not confirmed in subsequent multi-center studies.[62, 63] Several factors may have contributed to these disappointing results including the relatively low level of PDGFR activation in primary GBM tumors.

In the current study, imatinib and hydroxyurea was well-tolerated among recurrent LGG patients. The majority of adverse events were grade 2 while grade 3 events were uncommon and grade 4 toxicities were rare. The toxicity profile of this regimen appears comparable to that reported for various temozolomide regimens among recurrent/progressive LGG patients. [19-21, 40, 41]

However, outcome on the current study appears inferior to that reported for temozolomide. We observed no radiographic responses whereas the radiographic response rate reported among various temozolomide regimens is 20-61%.[19-21, 24, 40, 41] One potential factor contributing to this difference may be differences in criteria used to define radiographic response. For example, we required a partial response to include a 50% reduction of the FLAIR bi-dimensional product as well as any enhancing disease, whereas some of the other studies only assessed enhancing tumor. The accurate ascertainment of tumor growth control can be challenging to achieve among tumors where the natural history reflects indolent growth, such as LGG. In addition, the use of a numeric cut-off to define progression, such as a 25% increase in tumor dimension, can be misleading in that this practice allows tumors to be classified as stable, when in fact, they are progressively growing. Recently published recommendations for response assessment among LGG patients provide guidelines that will help ensure optimal and consistent assessment approaches for future LGG studies.[64]

In addition, the median PFS and PFS-12 rate observed on our study, 11 months and 39% respectively, were lower than most of the results reported for temozolomide therapy (Table 4).[19-21, 24, 40, 41] We evaluated several clinical factors previously shown to predict outcome for LGG patients and most were not associated with PFS, most likely reflecting the overall negative outcome on our study. Unfortunately, due to lack of archival tumor material, we were unable to assess whether PDGF/PDGFR expression or genetic abnormalities such as chromosome 1p/19q or IDH 1/2 mutations correlated with outcome. Another factor contributing to the low activity observed on the current study is that the distribution of imatinib into the brain in preclinical studies has been shown to be limited by P-glycoprotein mediated efflux.[65] Although imatinib has been shown to achieve intratumoral concentrations that are comparable to those measured in plasma among malignant glioma patients where the blood-brain-barrier is relatively defective,[66] the blood-brain barrier was likely intact for most of the patients in the current study given their low-grade histology. [67]Although our study demonstrated that imatinib, combined with hydroxyurea had negligible anti-tumor activity, PDGF and PDGFR remain noteworthy potential therapeutic targets for recurrent/ progressive LGG and studies evaluating other PDGF/PDGFR inhibitors should be considered.

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Table 1

Patient characteristics

	Cohort A[1] (n=32)	Cohort B[1] (n = 32)
Age (median; years)	39.3	46.2
Range (years)	24.3 – 83.8	22.6 – 67.2
Gender		
Male	20 (63)	19 (60)
Female	12 (38)	13 (40)
Histology		
Astrocytoma	32 (100)	0
Oligodendroglioma	0	28 (88)
Mixed Oligoastrocytoma	0	4 (12)
KPS		
91-100	18 (56)	21 (66)
80	10 (31)	9 (28)
60 – 70	4 (13)	2 (6)
AED Status		
EIAED	10 (31)	11 (34)
Non EIAED	14 (44)	18 (56)
No EIAED	8 (25)	3 (9)
Surgery, Prior to Enrollment		
Biopsy	4 (13)	9 (28)
STR	0	2 (6)
GTR	0	0
Time from Original Diagnosis		
Median (years)	2.53	5.84
Range (years	0.03 – 22.21	0.04 – 14.54
Prior Conventional XRT	5 (16)	6 (18)
Stereotactic Radiosurgery	0	1 (3)
Prior Chemotherapy		
Temozolomide	10 (31)	11 (34)
Carboplatin	0	1 (3)
PCV	0	1 (3)
BCNU Wafers	0	1 (3)
Number Prior Episodes of PD		
0	3 (9)	0
1	23 (72)	21 (66)
2	6 (19)	9 (28)
≥ 3		2(6)

	Cohort A[1] (n=32)	Cohort B[1] (n = 32)
Tumor > 6 cm	22 (69)	28 (88)
Tumor crossing midline	15 (47)	16 (50)
Presence of contrast enhancement	13 (41)	16 (50)

[1] A: Astrocytoma cohort; B: oligodendroglioma cohort

Abbreviations: AED, anti-epileptic drugs; BCNU, carmustine; EIAED, CYP3A enzyme-inducing anti-epileptic drugs; GTR, gross total resection; KPS, Karnofsky performance status; PCV, procarbazine, carmustine and vincristine; PD, progressive disease; STR, subtotal resection; XRT, radiation therapy

Table 2

Summary of treatment toxicity

Toxicity Cohort[1]	Grade 2		Grade 3		Grade 4	
	A	B	A	B	A	B
Anemia	2 (6)	1 (3)	1 (3)			
Anorexia	2 (6)	2 (6)				
Creatinine increase		1 (3)				
Diarrhea	5 (16)	3 (9)	1 (3)	1 (3)		1 (3)
Edema	2 (6)					
Fatigue	12 (38)	13 (41)		1 (3)		
Infection	4 (12)	3 (9)		1 (3)		
Mucositis	1 (3)					
Nausea	10 (31)	5 (16)	1 (3)	1 (3)		
Neutropenia		2 (6)	2 (6)	3 (9)	1 (3)	1 (3)
Rash	5 (16)	2 (6)				
Thrombocytopenia				2 (6)		
Transaminase elevation		1 (3)				
Weight loss				1 (3)		

*numbers in parentheses indicate percentage of treated patients

[1]A: astrocytoma cohort; B: oligodendroglioma cohort

Table 3

Summary of outcome

	Astrocytoma (n=32)	Oligodendroglioma (n=32)	All patients (n=64)
Median follow-up (weeks)	191.0 (174.0; 203.7) *	176.0 (147.0; 190.3)	179.9 (171.4; 192.1)
Progression-free survival			
Median (weeks)	43.5 (31.7, 63.7)	43.3 (24.9, 53.6)	43.5 (33.0, 53.6)
12 months (%)	43.8 (26.5, 59.8)	34.4 (18.8, 50.6)	39.1 (27.2, 50.7)
24 months (%)	21.9 (9.6, 37.2)	21.9 (9.6, 37.2)	21.9 (12.7, 32.6)
36 months (%)	9.4 (2.4, 22.3)	15.6 (5.7, 30.0)	12.5 (5.8, 21.8)
Overall survival			
Median (weeks)	Not estimable	Not estimable	Not estimable
12 months (%)	93.8 (77.3, 98.4)	100	96.9 (88.1, 99.2)
24 months (%)	87.5 (70.0, 95.1)	90.6 (73.7, 96.9)	89.1 (78.4, 94.6)
36 months (%)	74.7 (55.7, 86.5)	75.4 (54.6, 87.7)	75.5 (62.6, 84.5)

* Data in parentheses indicates 95% confidence intervals unless otherwise specified

Table 4

Assessment of factors relative to progression-free survival

Group	Total	# Failed	Median survival in weeks (95% CI)	6-month survival (95% CI)	12-month survival (95% CI)	24-month survival (95% CI)	Logrank p-value
Maximum tumor size ≤ 6cm	16	15	46.6 (8.1, 63.7)	68.8% (40.5%, 85.6%)	43.8% (19.8%, 65.6%)	12.5% (2.1%, 32.8%)	0.6061
Maximum tumor size > 6cm	48	43	41.4 (31.7, 53.6)	68.8% (53.6%, 79.8%)	37.5% (24.1%, 50.9%)	25% (13.9%, 37.8%)	
No tumor crossing the midline	33	28	49 (31.9, 64.3)	72.7% (54.1%, 84.8%)	45.5% (28.2%, 61.2%)	30.3% (15.9%, 46.1%)	0.0917
Tumor crossing the midline	31	30	41 (24, 44.9)	64.5% (45.2%, 78.5%)	32.3% (16.9%, 48.6%)	12.9% (4.1%, 27%)	
No presence of contrast	35	30	51.4 (41, 63.7)	80% (62.6%, 89.9%)	48.6% (31.4%, 63.7%)	28.6% (14.9%, 43.8%)	0.0673
Presence of contrast	29	28	37.7 (23.6, 46.4)	55.2% (35.6%, 71%)	27.6% (13.1%, 44.3%)	13.8% (4.3%, 28.6%)	
Age ≥ 40 years	38	34	45.9 (31.7, 56)	68.4% (51.1%, 80.7%)	42.1% (26.4%, 57%)	26.3% (13.7%, 40.8%)	0.3583
Age < 40 years	26	24	42.1 (24.6, 53.6)	69.2% (47.8%, 83.3%)	34.6% (17.5%, 52.5%)	15.4% (4.8%, 31.5%)	
KPS < 90	25	23	43 (24.9, 55.9)	64% (42.2%, 79.4%)	32% (15.2%, 50.2%)	20% (7.3%, 37.2%)	0.5713
KPS ≥ 90	39	35	46.4 (31.7, 63.7)	71.8% (54.9%, 83.3%)	43.6% (27.9%, 58.3%)	23.1% (11.4%, 37.1%)	
Astrocytoma	32	29	43.5 (31.7, 63.7)	71.9% (52.9%, 84.3%)	43.8% (26.5%, 59.8%)	21.9% (9.6%, 37.2%)	0.9434
Oligodendroglioma	32	29	43.3 (24.9, 53.6)	65.6% (46.6%, 79.3%)	34.4% (18.8%, 50.6%)	21.9% (9.6%, 37.2%)	
No use of EIAEDs	43	39	44 (33, 56)	67.4% (51.3%, 79.3%)	41.9% (27.1%, 55.9%)	23.3% (12%, 36.6%)	0.8876
Use of EIAEDs	21	19	41 (24.6, 55.9)	71.4% (47.2%, 86%)	33.3% (14.9%, 53.1%)	19% (5.9%, 37.7%)	
≤ 1 PD	49	43	49 (41.1, 63.7)	75.5% (60.9%, 85.3%)	46.9% (32.6%, 60%)	26.5% (15.2%, 39.3%)	0.0045
>1 PD	15	15	25.1 (15.6, 41)	46.7% (21.2%, 68.7%)	13.3% (2.2%, 34.6%)	6.7% (0.4%, 26%)	

Abbreviations: CI, confidence interval; cm, centimeter; EIAED, CYP3A-enzyme inducing antiepileptic drugs; KPS, Karnofsky performance status; PD, progressive disease

Table 5

Outcome on the current study relative to temozolomide studies for LGG.

Report (citation)	Design	Number of patients	Failed prior XRT (%)	Failed prior chemotherapy (%)	ORR (%)	Median PFS (months)	PFS-12 (%)
Current study	Prospective	64	11 (17)	24 (38)	0	11	39
Taal[19]	Prospective	58	58 (100)	0	25 (54)[1]	8	25
Kesari[21]	Prospective	44	12 (27)	0	9 (20)	38	91
Quinn[20]	Prospective	46	7 (15)	10 (22)	28 (61)	22	76
Tosoni[41]	Prospective	30	0	0	9 (30)	22	73
Pace[40]	Prospective	43	30 (70)	16 (37)	20 (47)	10	47
Kaloshi[24]	Retrospective	149	0	0	22 (15)	28	80

[1] 46 of 58 patients were evaluable for response;

Abbreviations: LGG, low-grade glioma; ORR, overall radiographic response rate; PFS, progression-free survival; PFS-12, progression-free survival at 12 months; XRT, radiation therapy;