Salvage Chemotherapy with Cyclophosphamide for Recurrent, Temozolomide-Refractory Glioblastoma Multiforme

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BACKGROUND. The primary objective of the current prospective Phase II study of cyclophosphamide (CYC) in adult patients with recurrent, temozolomide-refractory glioblastoma multiforme was to evaluate 6-month progression-free survival (PFS).

METHODS. Forty patients (28 men and 12 women) ages 28–67 years (median age, 51.5 years), with recurrent glioblastoma multiforme were treated. All patients had been treated previously with surgery and involved-field radiotherapy (median dose, 60 grays [Gy]; range, 59–61 Gy). In addition, all patients were treated adjuvantly with either nitrosourea-based chemotherapy (21 patients: procarbazine, lomustine, and vincristine in 13 patients; carmustine in 8 patients) or temozolomide (19 patients). Twenty-one patients who were treated previously with a nitrosourea were treated with temozolomide at the time of first recurrence. Twenty-one patients were treated with CYC at the time of second recurrence, and 19 patients were treated with CYC at the time of first recurrence. CYC was administered intravenously on 2 consecutive days (750 mg/m^2 per day) every 4 weeks (operationally defined as a single cycle). Neurologic and neuroradiographic evaluations were performed every 8 weeks.

RESULTS. All patients were evaluable. In total, 170 cycles of CYC (median, 2 cycles; range, 2–12 cycles) were administered. CYC-related toxicity included alopecia in all patients (100%), anemia in 6 patients (3.5%), thrombocytopenia in 7 patients (4.1%), and neutropenia in 9 patients (5.3%). Four patients required transfusions (two required red blood cell transfusion, and two required platelet transfusion). One patient developed neutropenic fever without bacteriologic confirmation. No treatment-related deaths occurred. Seven patients (17.5%; 95% confidence interval [95% CI], 8–33%) exhibited a neuroradiographic partial response, 11 patients (27.5%; 95% CI, 15–44%) had stable disease, and 22 patients (55%) had progressive disease after a single cycle of CYC. The time to tumor progression ranged from 2 months to 18 months (median, 2 months). Survival ranged from 3 months to 24 months (median, 4 months). In patients with either a neuroradiographic response or stable disease (n = 18 [45%]), the median time to tumor progression was 6 months (range, 4–18 months; 95% CI, 6–8 months), and the median survival was 10 months (range, 5–24 months; 95% CI, 8–10 months). The 6-month PFS rate was 20%.

CONCLUSIONS. CYC exhibited modest efficacy with acceptable toxicity in the current cohort of adult patients with recurrent glioblastoma multiforme, all of whom had previously experienced treatment failure after temozolomide chemotherapy. ***Cancer*** **2004;100:1213–20.** © *2004 American Cancer Society.*

KEYWORDS: cyclophosphamide, progression-free survival, recurrent glioblastoma multiforme, response.

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The treatment of recurrent high-grade glioma is problematic, because only partially effective therapeutic modalities are available. These treatment strategies include chemotherapy, radioactive implants, stereotactic radiotherapy, immunotherapy, and reoperation.[1–12] Chemotherapy for recurrent malignant primary brain tumors is of modest benefit, primarily because response to chemotherapy is palliative and limited in its duration. In an analysis of 8 institutional Phase II studies of chemotherapy for recurrent high-grade gliomas, Wong et al. reported that response rates in patients with recurrent glioblastoma multiforme (GBM) were 6%, and the progression-free survival rate at 6 months (6-month PFS) was 15%.[13] The agents that are most active are the nitrosoureas, such as carmustine (BCNU) and lomustine (CCNU), in addition to temozolomide (TMZ), procarbazine, *cis*-retinoic acid, and platinum compounds.[1,2,4,5,10–12,14,15] Another chemotherapeutic agent with purported activity in recurrent, high-grade gliomas is cyclophosphamide (CYC).[16,17]

The primary objective of the current single-institution, prospective Phase II trial was to observe whether CYC administered at a dose of 750 mg/m^2 per day for 2 consecutive days every 4 weeks could delay disease progression significantly in patients with recurrent GBM. Forty adult patients with recurrent, supratentorial GBM who were treated previously with surgery, radiotherapy, and at least one chemotherapy regimen containing TMZ and who were no longer responding to therapy were entered into the study.

MATERIALS AND METHODS

The current study was performed at the University of Southern California Norris Comprehensive Cancer Center and Hospital (Los Angeles, CA). The study was activated in November 1999 and closed in January 2003. Approval of the protocol and the informed consent process was received from the University Human Investigation Committee. Informed consent was obtained from each participant.

Objectives and Endpoints

The primary objective of the current study was to determine the efficacy and toxicity of CYC in the treatment of patients with TMZ-refractory recurrent or progressive GBM. The primary endpoint was 6-month PFS. Secondary endpoints included overall survival (OS), time to disease progression, and response. Toxicity was evaluated in all eligible patients who received at least one cycle of CYC.

Eligibility Criteria

Patients were required to have had histologically proven recurrent GBM, and they also were required to have experienced disease progression after receiving definitive radiotherapy and at least one previous chemotherapy regimen that included TMZ. At least 4 weeks were required to have elapsed since the last dose of chemotherapy (6 weeks for nitrosoureas), and eligible patients were required to have recovered from the adverse effects of previous therapy. Patients who previously received CYC therapy were ineligible. Eligible patients had radiographically measurable intracranial disease in which the recurrent tumor was bidimensionally measurable (at least 1 cm $\times$ 1 cm) by contrast-enhanced magnetic resonance imaging (MRI) of the cranium. Histologic confirmation of tumor recurrence was not required for entry into the study. Pregnant or lactating women were not allowed to participate. Patients of childbearing potential were required to implement adequate contraceptive measures during their participation in the study. An Eastern Cooperative Oncology Group performance status of 0–2 (Karnofsky performance status $\geq$ 60) and a life expectancy $>$ 3 months were required for all patients.

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 $\geq$ 60 mL/m^2/1.73).

All patients were aware of the neoplastic nature of their disease and willingly consented to participate after they were informed of the procedures to be used, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Patients with carcinomatous meningitis were not eligible. No serious concurrent medical illnesses or active infections could be present that would jeopardize the ability of the patient to receive CYC therapy. Patients could not have an active concomitant malignancy, except for skin carcinoma (squamous cell or basal cell). Patients ages 18–80 years were eligible for the study.

Imaging

Cranial magnetic resonance examinations were performed on a 1.5-tesla superconducting magnet (Signa; General Electric Medical Systems, Milwaukee, WI). Using a spin-echo pulse sequence, axial T_2-weighted (T_2W; repetition time [TR], 3000 msec; echo time [TE], 80 msec), proton density–weighted (TR, 3000 msec;

TE, 30 msec) images were acquired initially. Subsequently, both sagittal axial and coronal T_1-weighted (T_1W; TR, 600 msec; TE, 25 msec) 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, NJ), coronal, axial, and sagittal T_1W sequences (TR, 600 msec; TE, 25 msec) were obtained. All postcontrast images were obtained within 30 minutes of gadolinium infusion. A panel of two radiologists independently reviewed cranial contrast-enhanced MRI scans, as did the treating neurooncologist (M.C.C.).

Drug Schedule

All patients received CYC (Cytoxan; Meade Johnson Pharmaceuticals, Princeton, NJ) at a dose of 750 mg/m^2 administered intravenously over 30 minutes on 2 consecutive days. Concurrent dexamethasone was permitted for control of neurologic signs and symptoms. Premedication included ondansetron 0.15 mg/kg and dexamethasone 4.0 mg, both administered intravenously. Prechemotherapy hydration utilized 1 L of normal saline given intravenously over 2 hours.

Postchemotherapy medication included prochlorperazine for nausea or emesis. CYC administration (1500 mg/m^2) was repeated 4 weeks after the initial dose. A cycle of therapy was defined operationally as 28 days during which CYC was administered on Days 1 and 2. Treatment with CYC was repeated every 28 days from Day 1 provided that all hematologic toxicity from the previous cycle had resolved to $\leq$ Grade 2 and that all nonhematologic toxicity had recovered to $\leq$ Grade 1. If recovery had not occurred by Day 28, then the subsequent cycle of CYC was delayed until these criteria were met. All toxicities including hematologic due to CYC therapy were rated according to the National Institutes of Health Common Toxicity Criteria (Version 3.0).

No dose escalations were permitted. Doses were reduced by 25% for toxicities, and only 2 dose reductions were allowed. Patients who had Grade 3 toxicity of any type after 2 dose reductions were withdrawn from the study.

Oral dexamethasone was used concurrently in 26 patients and was administered at an increased dose to 8 patients who had clinical disease progression. The dexamethasone dose was decreased in six patients as patient clinical status permitted.

Method of Evaluation

Blood counts were obtained weekly, neurologic examination was performed every 4 weeks, and contrast-enhanced cranial MRI was performed every 8 weeks after the second cycle of CYC. Neuroradiographic response criteria, as defined by MacDonald et al., were used.[18] A complete response (CR) was defined as the disappearance of all enhancing or nonenhancing tumor on consecutive CT or MRI scans taken at least 1 month apart, with the patient being neurologically stable or improved and not receiving corticosteroids. A partial response (PR) was defined as a reduction of $>$ 50% in the size of tumor on consecutive CT or MRI scans taken at least 1 month apart, with the corticosteroid dose being stable or decreased and with the patient being neurologically stable or improved. Progressive disease (PD) was defined as an increase of $>$ 25% in the size of the tumor, the appearance of any new tumor on CT or MRI, or the worsening of the patient's neurologic condition with corticosteroid doses remaining stable or increasing. Stable disease (SD) was defined as any other situation.

In patients with SD, PR, or CR, two additional cycles of CYC were to be administered, after which patients were assessed again, as described above. Patients continued to receive CYC therapy until documentation of PD, at which time patients were withdrawn from the study and were either monitored or (for patients with PD) offered alternative therapy.

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

Statistical Considerations—Experimental Design

The primary objective was to determine whether CYC could delay disease progression significantly in patients with recurrent GBM. Historic values were obtained from analysis of a data base of 225 patients with recurrent, high-grade glioma (GBM) who were treated on consecutive prospective Phase II trials in which the 6-month PFS rate was 15% for patients with GBM.[13] The hypotheses tested were H_0 ($P = P_0$) versus H_1 ($P > P_1$), where P was the probability of remaining alive and progression free at 6 months, with an alpha of 10% and a beta of 5%. For GBM, P_0 was set at 10% and P_1 was set at 30%, with the goal of a 20% improvement. The current study was designed to accrue 40 patients with GBM. Success was defined as the observation of $>$ 7 of 40 patients alive and progression free at 6 months (yielding alpha + 4% and beta + 6%). Kaplan–Meier estimates for PFS and OS and their associated 95% confidence intervals (95% CIs) were computed.

TABLE 1
Recurrent Glioblastoma Multiforme: Salvage Therapy with Cyclophosphamide

				Adjuvant therapy											
						Chemotherapy			Previous salvage therapy			Cyclophosphamide salvage therapy			
Patient no.	Gender	Age (yrs)	Tumor location	Surgery	RT (Gy)	Agent	No. of cycles	Best response	Agent	No. of cycles	Best response	No. of cycles	Best response	Response duration (mo)[a]	Survival (mo)
1	F	28	Bi frontal	STR	60	PCV	3	SD	TMZ	6	SD	12	PR	18	24
2	M	29	L temporal	GTR	60	PCV	6	SD	TMZ	3	PD	8	SD	10	12
3	M	32	R frontal	GTR	60	BCNU	3	SD	TMZ	6	SD	2	PD		4
4	F	33	R parietal	Bx	59	TMZ	6	SD				2	PD		4
5	M	34	L parietal	Bx	60	PCV	2	PD	TMZ	4	PD	2	PD		4
6	F	35	R thalamus	Bx	60	PCV	4	SD	TMZ	4	SD	2	PD		4
7	F	36	R frontal	STR	60	PCV	4	SD	TMZ	4	SD	4	SD	4	6
8	M	38	R occipital	GTR	60	PCV	3	PD	TMZ	5	SD	8	SD	8	10
9	M	39	R temporal	STR	61	PCV	1	PD	TMZ	5	SD	2	PD		3
10	M	40	L frontal	GTR	60	PCV	4	SD	TMZ	4	SD	4	SD	4	6
11	F	42	R frontal	STR	59	PCV	4	SD	TMZ	3	SD	2	PD		3
12	M	43	L parietal	Bx	60	TMZ	4	SD				6	SD	6	10
13	M	44	R frontal	STR	60	TMZ	5	SD				2	PD		3
14	F	46	L occipital	GTR	59	PCV	3	SD	TMZ	4	SD	6	PR	6	10
15	F	47	L parietal	Bx	60	BCNU	1	PD	TMZ	3	SD	2	PD		3
16	M	48	R thalamus	Bx	60	TMZ	2	PD				2	PD		4
17	M	49	L insular	Bx	60	TMZ	6	SD				12	PR	12	16
18	M	50	R frontal	GTR	60	PCV	3	SD	TMZ	3	SD	6	SD	6	8
19	F	51	L frontal	STR	61	TMZ	6	SD				8	PR	8	10
20	M	51	L temporal	STR	59	BCNU	4	SD	TMZ	3	SD	4	SD	4	6
21	M	52	R occipital	STR	60	PCV	4	SD	TMZ	2	PD	2	PD		4
22	M	53	R frontal	GTR	60	TMZ	8	SD				6	SD	6	8
23	M	54	R temporal	STR	60	TMZ	6	SD				2	PD		3
24	M	55	L parietal	Bx	60	PCV	4	SD	TMZ	3	SD	2	PD		3
25	M	56	R frontal	STR	60	TMZ	6	SD				6	SD	6	8
26	M	57	R temporal	GTR	61	TMZ	8	PR				2	PD		3
27	F	57	L frontal	STR	59	TMZ	10	SD				2	PD		4
28	M	58	L temporal	GTR	60	BCNU	5	SD	TMZ	2	PD	2	PD		4
29	F	59	R temporal	STR	60	BCNU	4	SD	TMZ	4	SD	2	PD		3
30	M	59	R insular	STR	59	TMZ	8	SD				2	PD		4
31	M	60	L frontal	GTR	60	TMZ	10	SD				8	PR	8	10
32	M	61	R frontal	STR	60	TMZ	8	SD				2	PD		4
33	M	62	R frontal	GTR	60	BCNU	3	SD	TMZ	6	SD	2	PD		3
34	M	63	L insular	Bx	60	TMZ	6	SD				2	PD		4
35	F	63	R temporal	GTR	59	TMZ	8	SD				12	PR	12	14
36	M	64	L thalamus	Bx	60	TMZ	10	PR				2	PD		3
37	M	65	R frontal	GTR	60	BCNU	4	SD	TMZ	3	SD	4	SD	4	6
38	F	65	L frontal	STR	59	BCNU	2	PD	TMZ	4	SD	8	PR	8	10
39	M	66	L temporal	STR	60	TMZ	6	SD				4	SD	4	5
40	M	67	R occipital	GTR	60	TMZ	5	PR				2	PD		4

RT: radiotherapy; Gy: grays; M: male; F: female; R: right; Bi: bilateral; L: left; STR: subtotal resection; GTR: macroscopic total resection; Bx: biopsy; BCNU: carmustine; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; PD: progressive disease; SD: stable disease; PR: partial response.

[a] Duration refers to time to tumor progression.

RESULTS

Study Population

Forty patients (28 men and 12 women) ages 28–67 years (median age, 51.5 years) with recurrent GBM (Table 1) were treated with CYC. Recurrent GBM was defined by objective neuroradiographic progression (> 25% increase in tumor size) compared with prior baseline neuroradiographic images using the criteria reported by MacDonald et al. All patients underwent cranial MRI demonstrating PD within 2 weeks of CYC administration.

Patients presented at the time of tumor recur-

rence with the following signs and symptoms: increased intracranial pressure, as manifested by increasing headache (n = 22), worsening seizures (n = 8), altered mental status (n = 6), progressive hemiparesis (n = 8), new-onset homonymous hemianopsia (n = 2), or gait ataxia (n = 2). Among the eight patients with worsening seizures, seizure semiology was as follows: five patients had simple partial seizures, two had complex partial seizures, and one had secondarily generalized seizures. In total, 35 patients were receiving anticonvulsant therapy involving levetiracetam (n = 23), phenytoin (n = 10), or carbamazepine (n = 2). Patient performance status (Karnofsky scale) ranged from 60 to 100 (median, 80) at the time of documented tumor recurrence and initiation of CYC therapy. Tumor locations (including multilobar tumors) were as follows: frontal lobe (n = 16), temporal lobe (n = 9), parietal lobe (n = 5), occipital lobe (n = 4), insula (n = 3), and thalamus (n = 3). Thirty-nine patients had lobar tumors, and 1 patient had a multilobar tumor. Pathology reports were reviewed by a panel of two neuropathologists and confirmed that all tumors were GBM according to World Health Organization criteria.

All patients had undergone previous surgery, which included complete resection in 14 patients, partial resection in 16 patients, and biopsy only in 10 patients (Table 1). No patient underwent a second surgery before study entry.

All patients had been treated previously with adjuvant limited-field radiotherapy (Table 1), and all patients received conventional fractionated radiotherapy, which consisted of 1.8–2.0 grays (Gy) administered daily, with a median tumor dose of 60 Gy (range, 59–61 Gy). No patients were treated with stereotactic radiotherapy. Eight patients progressed during radiotherapy, as demonstrated by preradiotherapy and postradiotherapy cranial MRI comparisons.

All patients were treated adjuvantly with alkylator-based chemotherapy (Table 1), as follows: nineteen patients received TMZ (range, 2–10 cycles; median, 6 cycles); 13 patients received procarbazine, CCNU, and vincristine (range, 1–6 cycles; median, 4 cycles); and 8 patients received BCNU (range, 1–5 cycles; median, 3.5 cycles). Nineteen patients who experienced treatment failure following adjuvant nitrosourea-based therapy were treated at the time of first recurrence with TMZ (range, 2–10 cycles; median, 4 cycles). All patients were started on CYC immediately upon documentation of tumor progression after TMZ, as demonstrated by neuroradiographic progression and, in 60% of patients, clinical disease progression. The median time to the initiation of CYC after initial surgery was 8.5 months (range, 2–15 months). In total, 170 cycles of CYC were administered. Two cycles of CYC were administered to each patient. CYC was administered at the proscribed dose in all patients. No other antiglioma agents aside from dexamethasone were utilized during the study. All patients tolerated the 1-liter normal saline prehydration without difficulty.

TABLE 2
Temozolomide in Recurrent Glioblastoma Multiforme: Toxicity Data

Toxicity	Grade 3	Grade 4	Total
Alopecia	0	0	0
Anemia	6	0	6
Constipation	1	0	1
Fatigue	8	0	8
Granulocytopenia	8	1	9
Headache	1	0	1
Hemorrhagic cystitis	0	0	0
Infection, neutropenia	1	0	1
Leukopenia	10	1	11
Nausea	3	0	3
Seizures	1	0	1
Thrombocytopenia	6	1	7
Thrombophlebitis	1	0	1
Emesis	2	0	2
Total	48	3	51

Toxicity

Toxicity was recorded for all grades for all patients by type using the National Cancer Institute Common Toxicity Criteria (Version 3.0). Table 2 lists all Grade 3–4 toxicities observed, with each value representing the sum of the highest grade of toxicity attained per toxicity per cycle for all patients. A total of 170 treatment cycles were administered, and there were 48 (28%) Grade 3 adverse events (AEs) and 3 (1.8%) Grade 4 AEs. No Grade 5 toxicity was observed. The most common Grade 3–4 AEs were leukopenia (6.5%), granulocytopenia (5.3%), fatigue (4.7%), and anemia (3.5%).

All patients developed CYC-related alopecia. Four patients required transfusions, two with packed red blood cells and two with platelets. One patient developed febrile neutropenia; however, body fluid cultures were negative. No treatment-related deaths occurred.

Response

All patients were assessable for response. After 2 cycles of CYC (1500 mg/m^2 followed in 4 weeks by 1500 mg/m^2), 22 patients (55%) demonstrated PD. Thirteen patients (32.5%) received $\geq$ 6 cycles of therapy. At the conclusion of CYC, Karnofsky performance status ranged from 30 to 70, with a median of 60 in the entire

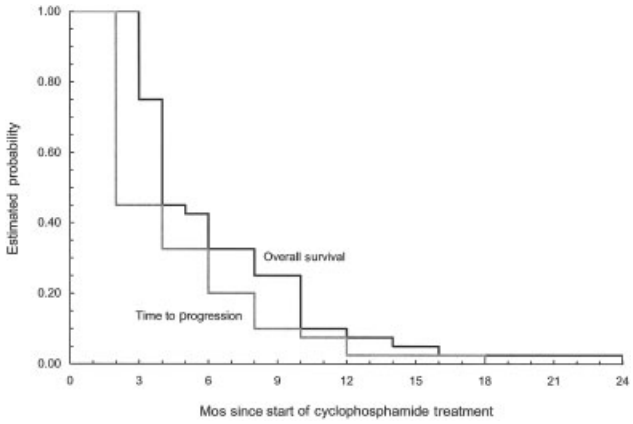

FIGURE 1. Association of survival and time to disease progression ($n = 40$ for both curves) with cyclophosphamide in adult patients with temozolomide-refractory glioblastoma multiforme.

study group. Patients who did not respond to CYC were offered alternative or supportive therapy. Survival in the entire cohort ranged from 3 months to 24 months, with a median of 4 months. Four patients (10%) survived $\geq$ 1 year. All patients have died, and all deaths were attributable directly to the effects of progressive intracranial tumor.

Seven patients (17.5%) experienced a neuroradiographic PR (95% CI, 8–33%), and 11 patients (27.5%) had SD (95% CI, 15–44%). In patients with either a neuroradiographic response or SD ($n = 18$ [45%]), the median time to tumor progression was 6 months (range, 4–18 months; 95% CI, 6–8 months), and the median survival was 10 months (range, 5–24 months; 95% CI, 8–10 months).

Among the seven patients who had a PR to CYC, four had been treated previously with a single chemotherapy regimen, and three had been treated previously with two chemotherapy regimens. The best response to prior chemotherapy among patients with responses to CYC was SD. Of the 11 patients with SD after CYC, 6 patients had responses that were $>$ 6 months in duration (3 patients with 1 prior chemotherapy regimen and 3 patients with 2 prior chemotherapy regimens). No difference was seen in pretreatment tumor volume between patients who had either a PR to CYC or SD and patients who had PD.

The overall PFS rate was 20% (95% CI, 8–32%) at 6 months and 2.5% at 1 year. The overall median time to tumor progression was 2 months (range, 2–18 months; 95% CI, 2–4 months) (Fig. 1). Regarding the primary endpoint of the study (6-month PFS), the results failed to exceed the 20% threshold for success, assuming a 20% improvement compared with the data base reported by Wong et al. (GBM: expected, 35%; observed, 20%).[13]

DISCUSSION

The treatment of recurrent GBM remains challenging. Notwithstanding the palliative benefit of resective surgery, the majority of patients are not candidates for reoperation. Furthermore, stereotactic radiotherapy strategies, such as radiosurgery or implantation, benefit a minority of patients, primarily because of the large size of recurrent GBM.[6,8,9] Therefore, palliation for the majority of patients who may be candidates for further therapy entails the administration of chemotherapy. Despite the recent introduction and success of TMZ, new chemotherapeutic agents are needed.

Wong et al. published an analysis of clinical outcomes in 225 patients with recurrent GBM who received chemotherapy in 8 consecutive, prospective Phase II trials. The overall 6-month PFS was only 15% for patients with recurrent GBM.[13] Two recent Phase II trials studied a similar patient group with recurrent or progressive GBM. Jaeckle et al. treated 40 patients with TMZ and 13 cis-retinoic acid and reported a 6-month PFS of 32%.[19] In their study, 48% of patients had been treated with 1 prior chemotherapy, and 53% had been treated with 2 prior chemotherapy regimens. The findings of Jaeckle et al. appear to represent an improvement compared with the randomized trial reported by Yung et al. in 119 patients with recurrent GBM comparing single-agent TMZ with procarbazine (the TMZ arm demonstrated a 6-month PFS of 21%).[20] Fine et al. treated 38 patients with the combination of BCNU and thalidomide and reported a 6-month PFS of 27%.[21] In their study, Fine et al. found that 50% of patients had been treated with 1 or 2 prior chemotherapy regimens, including 4 patients (10%) who previously had received nitrosourea-based treatment. Those authors reported that the activity of single-agent BCNU therapy for recurrent GBM was poorly documented, because prior trials using BCNU antedated contemporary CT or MRI brain imaging. Therefore, as the authors concede, the additive role of thalidomide to BCNU with respect to efficacy is uncertain.

The abovementioned trials, which were similar in design and patient number to the current study, suggest that combination chemotherapy may be superior to single-agent chemotherapy in the treatment of recurrent GBM. Clearly, proof of concept regarding polypharmacy will require evaluation in a randomized clinical trial rather than comparison with historic controls, issues both studies

stressed.[1,2,4,10] The current study focused on patients with GBM who previously had experienced treatment failure following chemotherapy (TMZ in 100% of patients, nitrosourea-based chemotherapy in 55% of patients) and for whom further treatment appeared to be warranted. The study did not require histologic proof of recurrent GBM, and the possibility of radiation necrosis rather than recurrent disease was possible. Nonetheless, this possibility appears to be unlikely, as no patient received stereotactic radiotherapy, and the risk of radiation necrosis was $< 5\%$ for patients who were treated with standard, fractionated radiotherapy. Furthermore, 10 patients underwent fluorodeoxyglucose-positron emission tomography, and 6 patients underwent magnetic resonance spectroscopy; in these patients, recurrent tumors were confirmed radiographically.

CYC appears to be an attractive option. Previous single-agent studies have suggested that CYC possesses activity against high-grade gliomas, and CYC is a core agent in the infant chemotherapy regimens that are in use today.[15–17,22] Furthermore, CYC toxicity is manageable (approximately 30% Grade 3–4 toxicity in the current study) and noncumulative, permitting administration without growth factor support. Finally, anticonvulsant medication (used almost universally in patients with GBM), in particular hepatic mixed-function cytochrome P450-inducing drugs, such as phenytoin and carbamazepine, up-regulate chemotherapy catabolism. This principle, which was articulated first by Fetell et al., results in chemotherapy underdosing, due to enhanced hepatic metabolism induced by heterocyclic anticonvulsant drugs.[23] The use of alkylator-based treatment strategies such as those involving CYC, which does not have pharmacodynamic interactions with enzyme-inducing anticonvulsant drugs, obviates this problem.

In conclusion, CYC administered according to the dosing and scheduling guidelines followed in the current study for patients with previously treated, TMZ-refractory, recurrent GBM appears to have limited benefit (6-month PFS, 20%). Regarding the primary endpoint of the study (6-month PFS), the results failed to exceed the 20% threshold for success, assuming a 20% improvement compared with the data base reported by Wong et al. (GBM: expected improvement, 30%; observed improvement, 20%[13]).

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