Phase I Study of Temozolomide and Escalating Doses of Oral Etoposide for Adults with Recurrent Malignant Glioma

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BACKGROUND. Although temozolomide is active against recurrent malignant glioma, responses in many patients are modest and short-lived. Temozolomide may prove more effective in combination with other agents. Therefore, combination oral chemotherapy for these patients is a particularly attractive approach.

METHODS. The authors conducted a Phase I study of temozolomide in combination with escalating doses of oral etoposide (VP-16) to determine the maximum tolerated doses of these two agents when given together. The temozolomide dose was fixed at 150 mg/m^2 per day on Days 1–5. The oral VP-16 was escalated in cohorts of 3 to 6 patients by numbers of days of VP-16 administered: 50 mg/m^2 per day, Days 1–5 (dose level 1), Days 1–8 (dose level 2), Days 1–12 (dose level 3), Days 1–16 (dose level 4), and Days 1–20 (dose level 5). Therapy was given in 28-day cycles.

RESULTS. Of the 29 patients enrolled, 26 were fully evaluable and 3 were partially evaluable for toxicity. The 29 patients received a total of 92 cycles. The median age of the patients was 49 years (range, 28–76 years). Diagnoses included glioblastoma (n = 19), gliosarcoma (n = 3), anaplastic astrocytoma (n = 5), and anaplastic oligoastrocytoma (n = 2). The median time from diagnosis to disease recurrence was 8 months (3–188 months). Twenty patients were treated at the first disease recurrence, seven at the second, and two at the third. Twenty-four patients (83%) were receiving anticonvulsants and 24 were receiving dexamethasone. All patients had received previous radiation, and 25 of 29 had been treated with chemotherapy previously. Of the 3 patients at dose level 1, none had dose-limiting toxicity (DLT). Of the 6 patients at dose level 2, 1 patient had DLT: Grade 3 thrombocytopenia resulting in a $>$ 2-week delay in starting the next cycle of chemotherapy. Of the 6 patients at dose level 3, 1 patient had DLT: death due to pneumonia. There were 2 DLTs in the 7 patients at dose level 4: fever, neutropenia, and herpes zoster infection in 1 patient and death due to pneumonia in another. Seven patients had been started at dose level 5 when DLT was established at dose level 4: of the 5 fully evaluable and 2 partially evaluable patients at dose level 5, there was no DLT.

CONCLUSIONS. The maximum tolerated dose of temozolomide and oral VP-16 in this heavily treated group of patients with recurrent malignant glioma is temozolomide 150 mg/m^2 per day for 5 days and oral VP-16 50 mg/m^2 per day for 12 days.
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KEYWORDS: temozolomide, etoposide, recurrent malignant glioma, oral chemotherapy.

Despite remarkable advances in surgery, radiotherapy, chemotherapy, and supportive care, the prognosis for patients with malignant glioma remains grim. The median survival for patients with glioblastoma multiforme has improved slightly over the past few

decades, with a median survival of approximately 12 months.[1] For patients with recurrent disease, the median survival period is only 6 months and only 10–20% of patients are disease progression free at 6 months from disease recurrence.[2] New approaches and new agents are desperately needed.

Temozolomide represents one such new approach. This drug renders its cytotoxic effect by methylating guanine in DNA at the N-7 and O-6 positions.[3] In animal models, temozolomide has been shown to penetrate the central nervous system (CNS).[4] This CNS penetration is substantiated by a number of studies of adults with newly diagnosed and recurrent malignant gliomas who have had MRI-documented responses to temozolomide.[5–11] Friedman et al.[9] reported responses in 16 of 36 patients (44%) with newly diagnosed high-grade gliomas and Yung et al.[11] documented a 35% complete response plus partial response rate in patients with recurrent anaplastic astrocytoma and anaplastic oligodendroglioma. Unfortunately, the responses are generally short-lived and the response rates in patients with recurrent glioblastoma are particularly poor.[12] Strategies being studied to improve the efficacy of temozolomide include the exploration of alternative schedules, the integration of temozolomide with radiotherapy, and the combination of temozolomide with other cytotoxic drugs.

Etoposide (VP-16) is a topoisomerase 2 inhibitor which, like temozolomide, penetrates the CNS and has activity against malignant brain tumors. Its efficacy is schedule dependent. Smaller doses over several days are more effective than single larger doses,[13] and higher response rates have been reported with small daily doses.[14,15] Orally administered VP-16 is effective against a variety of CNS tumors when administered as a 3-week course at a dose of 50 mg/m^2 per day.[14,15] Fulton et al.[16] used this schedule with oral VP-16 to treat 42 patients with recurrent malignant glioma. In that study, 8 responded and 11 had stable disease (SD).

We hypothesize that there may be synergy when temozolomide and VP-16 are used in combination. Lillie et al.[17] demonstrated a synergistic effect when VP-16 was added to the alkylating agents cyclophosphamide or melphalan to treat athymic mice with human rhabdomyosarcoma. Increased antitumor activity was also seen when irinotecan, another topoisomerase inhibitor, was added to carmustine or cyclophosphamide to treat human tumor xenografts derived from CNS malignancies.[18]

We conducted a clinical trial of combination therapy with temozolomide and VP-16. Because the 2 agents have not been given together, the trial was conducted as a Phase I study with a fixed dose of temozolomide (150 mg/m^2 per day once a day, Days 1–5) and a dose escalation of oral VP-16 (from 50 mg/m^2 per day on Days 1–5 to 50 mg/m^2 per day on Days 1–20). This combination holds great appeal because 1) both agents have established efficacy against high-grade tumors; 2) their mechanisms of cytotoxicity are different; 3) each is well tolerated when used as a single agent; and 4) both can be given orally, thus increasing their appeal to patients and treating physicians.

MATERIALS AND METHODS

Eligibility

Patients were eligible for the study if they were age $\geq$ 18 years and had recurrence or progression of glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, or mixed anaplastic oligoastrocytoma. Disease recurrence was defined as an increase in tumor size as documented on an MRI scan, biopsy-prone recurrence, or the presence of tumor cells in the cerebral spinal fluid (CSF). Patients were also required to have a World Health Organization (WHO) performance score of $\leq$ 2 and a life expectancy of $\geq$ 12 weeks. Chemotherapy and/or radiotherapy were allowed up to 4 weeks before enrollment. Patients were required to have an absolute neutrophil count (ANC) $\geq$ 1000 neutrophils per mm^3, a platelet count $\geq$ 100,000 platelets per mm^3, a hemoglobin level $\geq$ 10 g/dL, creatinine and bilirubin levels $\leq$ 1.5 times the upper limit of normal (ULN), levels of aspartate and alanine aminotransferase $\leq$ three times the ULN, and alkaline phosphatase $\leq$ two times the ULN. Patients were ineligible if they had other systemic diseases, frequent vomiting which could interfere with the ability to take oral medications, previous or concurrent malignancies (except basal or squamous cell carcinoma of the skin), or human immunodeficiency virus infection. Signed, written informed consent in accordance with guidelines of the institutional review board of each participating institution was required.

Treatment

All patients received a fixed dose of temozolomide, 150 mg/m^2 per day, once a day for 5 consecutive days (Days 1–5). They were instructed to fast from 1 hour before to 1 hour after taking the temozolomide. Patients also received VP-16, starting at 50 mg/m^2 per day orally, once a day for Days 1–5. The dose of VP-16 was escalated in cohorts of 3 to 6 patients by extending the number of days the dose of 50 mg/m^2 per day was given. Dose levels were escalated as follows: dose level 1, 5 days of VP-16; dose level 2, 8 days; dose level

3, 12 days; dose level 4, 16 days; and dose level 5, 20 days. Intrapatient dose escalation was not permitted. Cycles were repeated every 28 days and a maximum of 12 cycles was given.

If none of the first three patients enrolled at a given dose level developed dose-limiting toxicity (DLT), subsequent patients were enrolled at the next higher dose level. If DLT occurred in one of three patients, three additional patients were enrolled at that level. If one of six patients experienced DLT, the dose was escalated. If two or more of six patients had DLT at a given level, the maximum tolerated dose (MTD) was exceeded. The MTD was defined as one level below the level at which two or more of six patients developed DLT. Patients not completely evaluable for toxicity were replaced with additional patients.

Toxicity

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[19] Hematologic DLT was defined as Grade 4 neutropenia that lasted more than 7 days, Grade 4 anemia or thrombocytopenia that required transfusion on two occasions in 7 days, or as a delay of 14 days between treatment cycles. Nonhematologic DLT was defined as any chemotherapy-related Grade 3 or 4 nonhematologic toxicity with the specific exclusion of Grade 3 hepatotoxicity that returned to Grade 1 before the start of the next course of therapy.

Response

Although response was not an end point for the study, patients were evaluated for response by MRI scan every 8 weeks after even-numbered cycles.[20] A complete response was defined as the complete disappearance of the lesion(s) on MRI scan. A partial response (PR) was defined as a greater than 50% decrease in tumor size. A minor response (MR) was defined as a 25–50% decrease in tumor size as measured by the sum of the product of the maximum perpendicular diameters of all measurable lesions and no new lesions. Patients whose responses ranged from a 25% decrease to a 25% increase in tumor size were classified as having SD. Patients with a greater than 25% increase in tumor size, new lesions, or SD coupled with a neurologic deterioration were considered to have progressive disease (PD) and were removed from the study.

RESULTS

Twenty-nine patients were enrolled from four participating institutions. Twenty-six patients were fully evaluable for toxicity. Three were only partially evaluable: 1 patient at dose level 4 who inadvertently received granulocyte–colony-stimulating factor (G-CSF) and therefore could not be fully evaluated for severity and duration of neutropenia; 1 patient who did not have a complete blood count on Day 28 of her first and only cycle of therapy; and 1 patient who developed a skull osteomyelitits secondary to recent surgery and was therefore removed from the study on Day 3. The 29 patients received a total of 92 cycles of chemotherapy (median, 2 cycles; range, 1–12 cycles). Table 1 shows the demographic and clinical data for the 29 patients.

TABLE 1
Demographic and Clinical Data for the 29 Patients Enrolled in the Study

Characteristic	No. of patients (%)
Age (yrs)	
Median (49)	
Range (28–76)	
Gender	
Male	20 (69)
Female	9 (31)
WHO score	
0	14 (48)
1	8 (28)
2	7 (24)
Diagnosis	
Glioblastoma	19 (66)
Gliosarcoma	3 (10)
Anaplastic astrocytoma	5 (17)
Anaplastic oligoastrocytoma	2 (7)
No. of recurrences at enrollment	
First	20 (69)
Second	7 (24)
Third	2 (7)
Previous therapy	
Radiation	29 (100)
One chemotherapy regimen	18 (62)
Two chemotherapy regimens	7 (24)
Previous nitrosourea therapy	24 (83)
Time from diagnosis to study entry (mos)	
Median (8)	
Range (3–118)	
Dexamethasone	24 (83)
Anticonvulsants	24 (83)

WHO: World Health Organization.

Dose Limiting Toxicity

A summary of patients and DLT is presented in Table 2. None of the 3 patients at dose level 1 had DLT. One of 6 patients had DLT at dose level 2: Grade 3 thrombocytopenia that persisted for more than 14 days. At dose level 3, one of 6 patients had DLT; the patient was hospitalized for fever and neutropenia and died of *Pneumocystis carinii* pneumonia. Two of 7 patients at

TABLE 2
DLT by Dose Level

Dose level	VP-16 dose (mg/m^2/d)	Patients	DLT
1	50 × 5 days	3	0
2	50 × 8 days	6	1
3[a]	50 × 12 days	6	1
4	50 × 16 days	7[b]	2
5	50 × 20 days	7[c]	0

DLT: dose-limiting toxicity; VP-16: etoposide.

[a] Maximum tolerated dose.

[b] One patient was partially evaluable because she received granulocyte—colony-stimulating factor for neutropenia.

[c] Two patients were partially evaluable because of a failure to obtain a complete blood count on Day 28 (n = 1) and because of a wound infection on Day 3 that required the patient to be removed from the study (n = 1).

TABLE 3
Study DLT and Other Toxicities

	Study DLT				Other toxicity			
Characteristics	Grade 1	2	3	4	Grade 1	2	3	4
Neutropenia	1	1	4	2	0	0	0	0
Thrombocytopenia	5	1	4	0	0	0	0	0
Anemia	0	0	1	0	0	0	0	0
Infection	0	0	0	3	0	5	1	0
Thromboembolus	0	0	0	0	0	0	1	2
ALT	1	0	0	0	0	0	0	0
Nausea	3	0	0	0	0	0	0	0
Vomiting	1	1	1[a]	0	0	0	0	0
Constipation	0	1	0	0	0	0	0	0
Fatigue	3	0	0	0	3	1	1	0
Pain	0	0	0	0	0	0	1	0
Weight loss	1	0	0	0	0	0	0	0
Headache	1	0	0	0	5	0	0	0
Seizure	0	0	0	0	0	2	3	0
Other neurotoxicity	0	0	0	0	2	6	1	0

DLT: dose-limiting toxicity; ALT: alanine aminotransferase.

[a] Patient had Grade 3 emesis because oral VP-16 was not diluted. She tolerated all previous and subsequent doses when the doses were properly diluted.

dose level 4 suffered DLT: one of the patients had fever, neutropenia, and pneumonia of unknown cause, and died. The second patient was hospitalized for fever, neutropenia, and herpes zoster infection. Seven patients had already been enrolled on dose level 5 (5 were evaluable and 2 were partially evaluable), when it was learned that one of the patients at dose level 4 had inadvertently been given G-CSF for neutropenia. Because this patient could not be fully evaluated for duration and complications of neutropenia, he was replaced with a seventh patient at dose level 4. This seventh patient had the fever, neutropenia, and herpes zoster infection noted above. It is noteworthy that none of the 5 fully evaluable patients at dose level 5 had DLT. However, because there were 2 patients with DLT at dose level 4, the MTD was established at dose level 3. A full description of study drug-related toxicities and other toxicities is detailed in Table 3.

Responses to Therapy

Although response to therapy was not a formal outcome of the study, patients with residual disease were evaluated for response after every two cycles or if there was a clinical deterioration. One patient had a PR, another patient had an MR, 11 patients had SD, 11 had PD, and 5 were not evaluable for response. The median duration of response was 4 months (range, 2–12 + months).

DISCUSSION

The primary purpose of this Phase I study of combination oral chemotherapy was to determine the MTD of oral VP-16 when it was administered in combination with a fixed dose of temozolomide. We investigated whether sufficient amounts of each agent could be administered safely and achieve some degree of efficacy. There are well documented responses to each agent alone in patients with recurrent malignant glioma,[5–8,16] and there are in vitro data that suggest the possibility of synergy when an alkylator and topoisomerase inhibitor are used together.[18] There are also many benefits to finding a multiagent regimen that can be totally orally administered.

We escalated the dose of VP-16 by the number of days administered rather than by increasing the amount given for each daily dose. The rationale for this approach is based on data published by Rellig et al.,[21] which showed that cytotoxic levels of VP-16 in the CSF were not achieved until patients received a daily oral dose of 50 mg/m^2. Therefore, a dose lower than 50 mg/m^2 per day over an extended period may not have reached cytotoxic levels in the CNS. The lower dose of temozolomide (150 mg/m^2 for 5 days) is likely to have some effectiveness even when given alone. In some studies, patients are started on this lower dose and only escalated to the higher dose of 200 mg/m^2 per day for 5 days if they tolerate the lower dose.[11,12] In a few studies, patients who received previous therapy with nitrosoureas remained at the 150 mg/m^2 per day dose and responses at this lower dose have been reported. [22]

Overall, this regimen was reasonably well tolerated. Most of the serious study drug-related toxicities were hematologic or infectious. There were several serious adverse events, most notably two patients who died of pneumonia (one with P.*carinii* pneumonia, one of unknown cause) and one patient who was

hospitalized for fever, neutropenia, and herpes zoster infection. Although the functional status of these patients had been good (WHO score of 0), all 3 had received previous chemotherapy and all 3 were receiving dexamethasone. Most of our patients were receiving dexamethasone and were lymphopenic at the time of enrollment on the study. The dexamathasone likely heightened the risks of developing *P. carinii* pneumonia and herpes zoster infection. A number of reports have documented the increased frequency of *P. carinii* pneumonia in patients with brain tumors.[23,24] It is likely that the combination of chemotherapy and dexamethasone heightens the risk of these patients developing opportunisitc infections. For the Phase II portion of our study, we require all patients to receive *P. carinii* pneumonia prophylaxis.

We enrolled 5 fully evaluable patients at dose level 5 (20 days of oral VP-16), 2 dose levels above the MTD of temozolomide plus oral VP-16. These patients had already been enrolled when we learned that a patient at dose level 4 had been given G-CSF because of an ANC of 218 per mm^3 (the patient was well and afebrile and had no other drug-related toxicity). We believed that this patient was not fully evaluable because we were unable to document the true nadir of the ANC, the duration of the neutropenia, or any potential complications of the neutropenia. Two other patients (1 at dose level 3 and 1 at dose level 4) had been neutropenic and died of infections during their neutropenic periods. We believed it was imperative to replace this partially evaluable patient with a seventh patient at dose level 4. This seventh patient subsequently developed DLT: fever, neutropenia, and herpes zoster infection. We surpassed the MTD at dose level 4 and established the MTD at dose level 3: temozolomide, 150 mg/m^2 per day for 5 days (Days 1–5) plus VP-16, 50 mg/m^2 per day for 12 days (Days 1–12).

It is noteworthy that none of the 5 fully evaluable patients at dose level 5 developed DLT. This inconsistency is quite possibly due to chance. There were small numbers of patients enrolled at each dose level, as is the case for most Phase I trials. Even though these 5 patients did quite well at the higher doses of VP-16, the serious toxicity encountered at the lower dose levels mandated establishing the MTD at dose level 3. The MTD established in this study for patients with recurrent malignant gliomas may differ from the MTD for patients with other malignancies. Patients with other malignancies who have been less heavily treated and who are not receiving dexamethasone may tolerate higher cumulative doses of the oral VP-16.

To summarize, the MTD of oral VP-16 in conjunction with temozolomide at 150 mg/m^2 per day for 5 days is 50 mg/mg^2 per day for 12 days. We are currently conducting a Phase II trial of this combination at this dose to assess efficacy and to further evaluate toxicity in this group of patients.

REFERENCES

1. Levin VA, Leibel SA, Gutin PH. Neoplasms of the central nervous system. In: DeVita VT, Hellman S, Rosenberg SA. Cancer – principles and practice of oncology, 6th edition. Philadelphia: Lippincott Williams & Wilkins, 2001:2100–2160.
2. Yung WK, Albright RE, Olson J, et al. A phase I study of temozolomide versus procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer.* 2000;83:588–593.
3. Newlands ES, Stevens FMG, Wedge SR, Wheelhouse RT, Brock C. Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. *Cancer Treatment Rev.* 1997;23:35–61.
4. Brindley CJ, Antoniw P, Newlands ES. Plasma and tissue disposition of mitozomide in mice. *Br J Cancer.* 1986;53:91–97.
5. Newlands ES, Blackledge GRP, Slack JA, et al. Phase I trial of temozolomide. *Br J Cancer.* 1992;65:287–291.
6. O'Reilly SM, Newlands ES, Glaser MG, et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumors. *Eur J Cancer.* 1993;29A:940–942.
7. Newlands ES, O'Reilly SM, Glaser M, et al. The Charing Cross experience with temozolomide in patients with gliomas. *Eur J Cancer.* 1996;32A:2236–2241.
8. Bower M, Newlands ES, Bleehan NM, et al. Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemother Pharmacol.*1997;40:484–488.
9. Friedman HS, McLendon RE, Kerby T, et al. DNA mismatch repair and O-6 alkylguanine-DNA alkyltransferase analysis and response to Temodol in newly diagnosed malignant glioma. *J Clin Oncol.* 1998;16:3851–3857.
10. Gilbert M, O'Neill A, Grossman S, et al. A phase II study of preradiation chemotherapy followed by external beam radiotherapy for the treatment of patients with newly diagnosed glioblastoma multiforme: an Eastern Cooperative Oncology Group study (E2393). *J Neurooncol.* 2000;47:145–152.
11. Yung WK, Prados MD, Yaya-Tur R, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. *J Clin Oncol.* 1999;17:2762–2771.
12. Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma at first relapse. *Ann Oncol.* 2001;12:259–266.
13. Slevin ML, Clark PI, Joel SP, et al. A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. *J Clin Oncol.* 1989;7:1333–1340.
14. Ashley DM, Meier L, Kerby T, et al. Response of recurrent medulloblastoma to low-dose oral etoposide. *J Clin Oncol.* 1996;14:1922–1927.
15. Needle MN, Molloy PT, Geyer JR, et al. Phase II study of daily oral etoposide in children with recurrent brain tumors and other solid tumors. *Med Pediatr Oncol.* 1997;29:28–32.
16. Fulton D, Urtasun R, Forsyth P. Phase II study of prolonged oral therapy with etoposide for patients with recurrent malignant glioma. *J Neurooncol.* 1996;27:149–155.

17. Lilley ER, Rosenberg MC, Elion GB, Colvin DM, Bigner DD, Friedman HS. Synergistic interactions between cyclophosphamide or melphalan and VP-16 in a human rhabdomyosarcoma xenograft. *Cancer Res.* 1990;50:284–287.
18. Coggins CA, Elion GB, Houghton PJ, et al. Enhancement of irinotecan activity against central nervous system tumor xenografts by alkylating agents. *Cancer Chemother Pharmacol.* 1998;41:485–490.
19. National Cancer Institute. Common toxicity criteria, version 2.0. In: Common toxicity criteria manual. Bethesda: National Cancer Center Institute Cancer Therapy Evaluation Program, 1999.
20. McDonald DR, Cascino TL, Schold SC, et al. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* 1990;8:1277–1280.
21. Rellig MV, Mahmoud HH, Pui CH, et al. Etoposide achieves potentially cytotoxic concentrations in CSF of children with acute lymphoblastic leukemia. *J Clin Oncol.* 1996;14:399–404.
22. Brandes AA, Ermani M, Basso U, et al. Temozolomide as a second-line systemic regimen in recurrent high-grade glioma: a phase II study. *Ann Oncol.* 2001;12:255–257.
23. Schiff D. Pneumocystis pneumonia in brain tumor patients: risk factors and clinical features. *J Neurooncol.* 1996;27:235–240.
24. Stupp R, Dietrich PY, Osterman-Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concommitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol.* 2002;20:1375–1382.