



Phase II study of salvage therapy with high-dose tamoxifen and oral etoposide for recurrent malignant glioma

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Background: Salvage chemotherapy regimens for patients with recurrent glioma are limited in their efficacy. Reports of antitumor activity of the oral agents etoposide (VP-16[®], Immunex Corporation) and high-dose tamoxifen (Nolvadex[®], AstraZeneca) prompted this Phase II study. Tamoxifen and etoposide may be synergistic in their antitumor effects. Both agents are administered orally, are well tolerated individually and do not have overlapping toxicities. We report the results of a Phase II study of this combination as salvage therapy for patients with recurrent glioma. **Methods:** Patients received tamoxifen at an escalating dose from 120 mg/day to 240 mg/day over a 1-week period, after which time etoposide 50 mg/m²/day for 3 weeks was added to the regimen. Patients remained on tamoxifen continuously and the etoposide was repeated after a 2-week break. This 10-week cycle was repeated until tumor progression or unacceptable toxicity occurred. Response assessments using neuroradiographic imaging and clinical evaluation were performed every 10 weeks. **Results:** A group of 40 patients (31 males) were treated with this protocol. The median age was 45 years (range 17–71 years) and the median Karnofsky performance status was 80. Of these patients, 17 had glioblastoma multiforme, 14 had a Grade 3 tumor, eight had a Grade 2 tumor and one patient's tumor type was not specified. Patients represented a heavily pretreated group, with 35% having received two prior chemotherapy regimens and 60% having received at least three prior regimens. There was one complete, three partial and seven stable disease responses (total 27%). Median time to tumor progression was 2 months (approximately 1.4–2.3) and median survival for the cohort was 5 months (approximately 4.4–8.8). Three patients were alive at last contact beyond 3 years (two anaplastic astrocytoma and one oligoastrocytoma). The 6-month progression-free survival was 10%. Treatment was well tolerated, with no Grade 3 or 4 hematologic toxicities observed. **Conclusion:** This drug combination was well tolerated but had limited efficacy in this group of heavily pretreated patients with recurrent glioma.

Primary malignant gliomas are treated with surgical resection, radiation therapy and chemotherapy. The median survival time is approximately 50 weeks for patients with newly diagnosed glioblastoma multiforme and 150 weeks for patients with newly diagnosed anaplastic astrocytoma. Median survival for patients with recurrent malignant glioma that has progressed after initial radiation therapy is 4 to 12 months [1,2]. Most forms of salvage therapy rely upon chemotherapeutic approaches, yet few such agents provide any measure of success. The most commonly used drugs include the nitrosoureas, temozolomide (Temozol[®], Schering-Plough) and procarbazine. New agents are needed for treatment of this group of patients. Reports on the use of the two agents tamoxifen (Nolvadex[®], Astra Zeneca) and oral etoposide (VP-16[®], Immunex Corporation) in patients with recurrent glioma prompted this Phase II study.

Etoposide, a semisynthetic derivative of the plant substance podophyllotoxin, acts specifically in the late S phase and early G2 phase of the cell cycle by forming a complex with DNA topoisomerase II [3]. DNA topoisomerase II is an enzyme that prevents DNA from tangling during replication, by catalyzing double-strand breakage and reunion to relieve superhelical stress. Etoposide stabilizes the DNA-topoisomerase II complex, prevents the DNA strands from rejoining, causes subsequent double-strand breaks and kills cells in the process of DNA replication. Etoposide can be administered by a number of routes [4–6]. An oral preparation is available, allowing for chronic daily dosing schedules to be administered [4,7]. Prolonged exposure to a critical etoposide concentration would be expected to enhance the antineoplastic activity of the drug, both by the cell-cycle-specific mechanism of action and by

Keywords:
chemotherapy, etoposide,
glioma, recurrent, tamoxifen



prolonging its interaction with topoisomerase II. Etoposide is widely used in a variety of cancers, mainly small cell lung carcinoma, germ-cell tumors, leukemia and lymphomas [8]. Activity of oral etoposide in brain tumors of various histologic types has been reported [9–12]. In addition, high-dose etoposide as well as intracarotid administration have also been tested in malignant brain tumors [13–15].

The most relevant property of tamoxifen related to glioma cell proliferation is the inhibition of protein kinase C (PKC), an important enzyme in signal transduction [16–20]. *In vitro* studies have shown that the activity of PKC is critically correlated with glioma cell proliferation. Tamoxifen and its metabolites, specifically *N*-desmethyltamoxifen, are inhibitors of proliferation in cultured glioma cells [21]. Although the penetration of tamoxifen and its active metabolite into both normal brain and brain tumors is excellent, the kinetics of PKC activation in malignant gliomas may require high doses of tamoxifen [22]. At oral tamoxifen doses of 120 to 125 mg/m² twice daily, the average plasma concentration of tamoxifen and its active metabolite approximates the concentration required for *in vitro* inhibition of PKC. Several clinical studies have reported antiglioma activity with high-dose continuous tamoxifen, with good patient tolerability [23–27].

Multidrug resistance (MDR) is a form of cellular resistance to chemotherapy involving a number of commonly used drugs, one of which is etoposide, where reduced intracellular drug accumulation results from expression of a cell-membrane glycoprotein, P-glycoprotein [28–30]. P-glycoprotein mediates resistance to natural product antineoplastic agents through an active transport process, resulting in a reduced intracellular concentration of these agents. There is laboratory evidence of the amplification and expression of a MDR gene in human glioma cell lines [31,32]. A recent study also demonstrated a role for PKC in MDR in human glioma cell lines [33]. PKC appears to be involved in P-glycoprotein phosphorylation, which regulates its biological function. Inhibitors of PKC decrease phosphorylation of P-glycoprotein. Both tamoxifen and its principal metabolite, *N*-desmethyltamoxifen, are active as MDR modulators and, interestingly, also inhibit PKC activity.

The rationale for the evaluation of this combination of agents includes the facts that these agents have been demonstrated to be active as single agents in malignant glioma, do not have similar toxicities that would preclude the administration

of the individual agents at therapeutic concentrations and may in fact be synergistic based on the MDR-modulating activity of tamoxifen on etoposide [34–36]. Both agents are also well tolerated and easily administered as oral agents.

The objectives of this study were to assess the response rate and duration of response in patients with evaluable recurrent malignant gliomas treated with high-dose tamoxifen and oral etoposide and to assess the toxicities of the combination of these agents.

Patients & methods

Patient eligibility

Patients were at least 16 years of age, had a Karnofsky performance status (KPS) score of 60 or greater and must have had prior histologic documentation of a primary glioma. Patients must have been treated with radiation therapy and, if the initial histology was low grade, prior nitrosourea-based chemotherapy must have been used. Patients must have had documentation of progressive tumor and had recovered from prior therapy. There was no limit on the number of prior therapies. Normal hematologic, renal and hepatic parameters were required. Previous history of deep vein thrombosis or pulmonary emboli was not a specific exclusion criterion but patients were not on any active treatment for thromboembolic disease. Concomitant corticosteroids and anti-epileptic agents were allowed. All patients gave informed consent. The Committee on Human Research at the University of California (CA, USA) approved this protocol.

Treatment plan

Tamoxifen was administered orally on a daily basis at a dose of 120 mg/day for 1 week. If this was tolerated, the dose was then increased to a maximum of 240 mg/day, at which time etoposide was administered orally at 50 mg/m²/day for 3 weeks with a 2-week break. Patients received 6 weeks of etoposide treatment in a 10-week cycle. The etoposide schedule was then repeated, with a 10-week period constituting one cycle. Therapy was continued as described for four cycles or until documented tumor progression or toxicity that persisted despite dosage reduction. If a patient continued to respond without significant toxicity, further treatment was at the discretion of the treating physician.

Dosage modifications

Dosage modifications were based on hematologic, neurologic, or other organ toxicities. For hematologic toxicities, etoposide was adjusted based on

absolute neutrophil count and platelet count; modifications ranged from reduction to a half dose to discontinuation of etoposide treatment, depending on the counts.

If there was any evidence of grade 3 or 4 neurotoxicity at 240 mg/day for tamoxifen, the drug was discontinued for a maximum of 2 weeks until the toxicity was grade 1 or less and then could be reinstated at 180 mg/day. If grade 2 or 3 neurotoxicity developed at the reduced dose, tamoxifen was again stopped for a maximum of 2 weeks and when the toxicity was grade 1 or less, a second and final dose reduction to 120 mg/day was allowed. If any further grade 2 or higher neurotoxicity occurred at this dose, the patient was removed from the study. If any patient required longer than 2 weeks to recover to grade 1 or less, or in the case of grade 4 neurotoxicity, the patient was removed from the study.

If patients experienced grade 3 mucositis or diarrhea, etoposide dose was reduced by 50% until recovery. If grade 4 toxicity occurred, the patient was taken off the study. If grade 2 or more toxicity for nausea and vomiting occurred at a dose of 240 mg/day of tamoxifen, despite anti-emetics, the drug was discontinued until the toxicity was grade 1 or less, at which time the tamoxifen could be resumed at 180 mg/day. Further reduction to a minimum of 120 mg/day took place if any further grade 2 or higher gastrointestinal (GI) toxicity occurred and the patient recovered in 2 weeks or less. If any patient required longer than 2 weeks to recover to grade 1 or less, or in the case of grade 4 GI toxicity, the patient was removed from the study.

If patients developed any visual symptoms, tamoxifen was discontinued and a formal ophthalmologic examination was carried out. If any grade 3 toxicity other than those described above developed at a tamoxifen dose of 240 mg/day, the drug was held for a maximum of 2 weeks until the toxicity was less than grade 2, at which time the dose was resumed at 180 mg/day. A further reduction was allowed to 120 mg/day with the same parameters as above should further toxicity be encountered. If any patient required longer than 2 weeks to recover to grade 1 or less, or in the case of grade 4 toxicity, the patient was removed from the study.

Response assessment

Assessment of response occurred after each cycle of therapy, during week 10. Overall response was based on a combination of neurological and neuroradiographic evaluation as previously reported [37]. For patients to have been considered to have a

stable or better response, they must have been receiving stable or decreasing doses of dexamethasone, with radiographic and clinical improvement or stability.

In brief, a comprehensive neurological examination was performed every 10 weeks and evaluation was based on any changes in the neurological clinical exam from the previous examination. A score of +2 was classified as definitely better, +1 as possibly better, 0 unchanged, -1 as possibly worse and a score of -2 as definitely worse. The neuroimaging (magnetic resonance imaging [MRI]) criteria for response of measurable lesions were as follows: complete response (CR) was defined as the disappearance of all enhancing tumor; partial response (PR) was defined as greater than or equal to a 50% reduction in the product of the largest perpendicular diameters of contrast enhancement and no new lesions may arise; progressive disease (PD) was defined as greater than or equal to a 25% increase in the product of the largest perpendicular diameters of contrast enhancement or any new enhancing tumor on MRI scans; and stable disease (SD) was defined as all other situations.

Endpoints & statistical considerations

The study would be considered worth pursuing if the observed response rate was 30% or better. Response was defined as SD or disease response lasting for at least 10 weeks for patients with glioblastoma and 20 weeks for patients with anaplastic or low-grade astrocytoma. If the true response rate was 40%, a sample size of 40 would assure that the chance of an observed response rate of less than 30% was less than 10%. We assumed that the study drug combination would be equally effective for recurrent glioblastoma multiforme or recurrent anaplastic astrocytoma after radiation therapy and recurrent astrocytoma after radiation therapy and at least one prior chemotherapy regimen. To ensure safety, if two or more patients of the first 14 accrued developed any grade 3 or 4 nonhematologic toxicity, accrual would have been discontinued. If three or more patients of the first 14 accrued had to be removed from study because of any toxicity, accrual would also have been discontinued.

Results

Patient population

Patient characteristics are shown in Table 1. In total, 40 patients were enrolled in the study. The median age was 45 years (range 17–71 years). Of

Table 1. Patient characteristics.

	n	%
Gender		
Male	31	78
KPS		
At least 80	28	70
60–70	12	30
Histology at initial diagnosis		
Glioblastoma multiforme	17	43
Grade 3	14	35
Grade 2	8	20
Not otherwise specified	1	2

Age at time of enrollment (years); Median: 45, Range: 17–71, n = 40.

KPS: Karnofsky performance status.

these patients, 70% had a KPS of at least 80. Recurrent glioblastoma multiforme was present in 43% of patients and low-grade tumors in 20%. The number of patients who had undergone prior chemotherapy is demonstrated in Table 2. The majority had at least two prior chemotherapy regimens and this population represents a heavily pretreated group of individuals. Of those enrolled, one patient refused therapy and died a little over 2 months later; this patient is included in the analysis. Only three patients were not receiving any anti-epileptic agents; of the others, one patient was taking a nonenzyme-inducing anti-epileptic drug, one was taking a combination of enzyme-inducing and nonenzyme-inducing anti-epileptic drugs and the remaining were taking enzyme-inducing anti-epileptic drugs.

Toxicity

Toxicities observed during the trial are shown in Table 3. The combination therapy was well tolerated. No patient had a history of thromboembolic disease prior to protocol enrollment. Two patients discontinued therapy due to the development of deep vein thrombosis (DVT). One patient had an

Table 2. Prior therapy.

Therapy	n (n = 40)	%
RT + nitrosourea	32	80
RT + non-nitrosourea	8	20
Number of prior chemotherapy regimens		
1	11	28
2	20	50
3	4	10
4	5	12

inferior vena cava filter placed. One patient stopped tamoxifen because of a stroke that was thought to be related to prior radiation therapy, not to the tamoxifen. There were no grade 3 or higher hematologic toxicities. There were 20% grade 2 and 3% grade 3 CNS toxicities manifested by ataxia and dizziness. These reversed with the discontinuation of tamoxifen.

Response, progression & survival

Including all patients in the analysis, there was one CR, three PRs and seven stabilization of disease, for a total response rate of 27% (2% CR, 7% PR and 18% stabilization of disease). The corresponding histology for the patients with SD or better is presented in Table 4. Of the patients, 29 had progressive disease (73%). The median time to tumor progression was 2 months and the median survival was 5 months. Six-month progression-free survival was 10%. Three patients were alive at last contact beyond 3 years (two anaplastic astrocytoma and one oligoastrocytoma). Kaplan–Meier estimates of survival are shown in Figure 1.

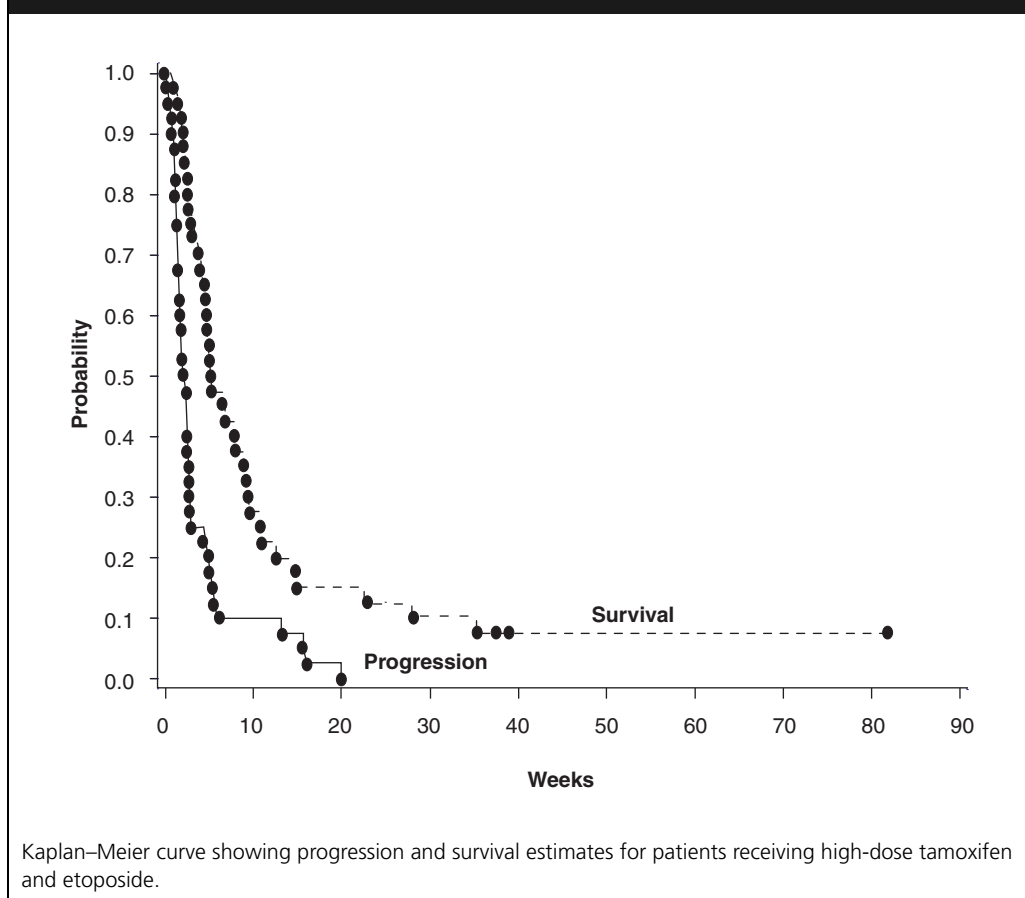
Including only patients with high-grade glioma, the median progression-free survival was 2.4 months (approximately 1.5–2.5 months) and 6-month progression-free survival was 10%. Three patients had progression-free survival of 13, 16 and 16 months, respectively. All patients had progressed at the time of this analysis. Median survival was 5.3 months (4.4–8.8 months). Six-month survival was 48%. Two patients were still alive at 37 and 82 months. These figures do not differ significantly from the analysis including patients with low-grade glioma. Kaplan–Meier estimates of survival for patients with high-grade glioma only are shown in Figure 2.

Discussion

In addition to its well-accepted effects on PKC activity, tamoxifen has multiple effects on the pathogenesis of glioma growth. These include the interaction with neu/c-erbB-2 receptors and subsequent inhibition of growth [38] and the influence on the levels of transforming growth factor- β 2 [39]. Preclinical studies suggest a complex interaction of this drug with multiple signaling pathways relevant to glioma growth and progression. Of interest for this particular study was the data suggesting that tamoxifen also has MDR-reversal capabilities [34–36,40,41].

Single-agent etoposide has been evaluated for the treatment of malignant glioma. Oral low-dose continuous administration, intracarotid delivery

Figure 1. Kaplan–Meier estimates of survival.



and a high-dose schedule in conjunction with stem-cell rescue have been reported [9–15]. This particular chemotherapeutic agent is well known to be involved in the MDR pathway that confers chemotherapy resistance to tumors. Drug resistance is a well known reason for the ineffectiveness of agents for the treatment of glioma [42,43]. High-dose tamoxifen as an enhancer of etoposide cytotoxicity has been evaluated in preclinical models as well as in clinical practice [34–36] and was a significant rationale for the combination with etoposide in glioma patients.

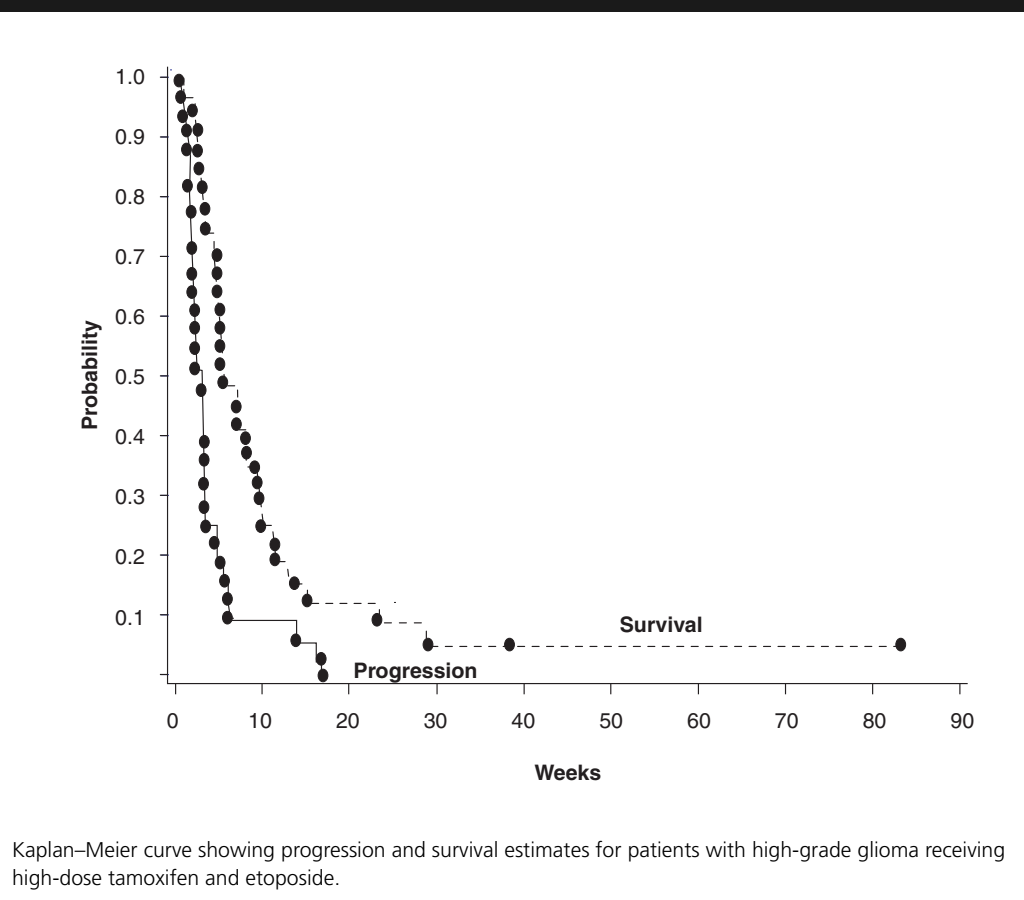
We report the results of this Phase II study of tamoxifen and etoposide in patients with recurrent malignant glioma. These patients had been previously treated with radiation therapy and, for the majority, multiple prior chemotherapy regimens. The treatment was well tolerated and disease stabilization or response was seen in 27% of the patients (2% CR, 7% PR and 18% stabilization of disease). Six-month progression-free survival was 10% with a median survival of 5 months. Comparison of these results to previously described studies in patients with recurrent malignant glioma is difficult for several reasons. Current brain tumor literature refers to treatment at the time of first or second tumor recurrence, compared with the patients in this trial who had failed three or more therapies problematic. This study also had a slight selection bias towards younger patients who have a better prognosis and included patients with an initial diagnosis of low-grade glioma who progressed despite radiation therapy and nitrosourea chemotherapy. Most investigational Phase II studies are conducted in patients with recurrent

Table 3. Toxicities observed.

Therapy	Grade (%)			
	1	2	3	4
Neutropenia	18	13	0	0
Thrombocytopenia	10	0	0	0
CNS (ataxia, dizziness)	10	20	3	0
Fatigue	10	3	0	0
Thromboembolism (DVT)	0	0	5	0

DVT: Deep vein thrombosis.

Figure 2. Kaplan-Meier estimates of survival for patients with high-grade glioma.



malignant glioma, that is in patients who had a previous histologic confirmation of either an anaplastic tumor (grade 3) or glioblastoma multiforme (grade 4). In fact, patients with an initial diagnosis of low-grade glioma are often excluded from clinical trials unless there is subsequent tissue confirmation of a higher-grade tumor. Recurrent 'low-grade' tumors, especially in the setting of multiple treatment failures,

have an aggressive clinical course; however, an appropriate historical control is lacking in the literature with which we can compare our results. In this study, the assessment of efficacy in the recurrent malignant glioma cohort only did not appear different compared with the group as a whole. Prospective clinical trials exploring new agents in this patient population of relapsed low-grade glioma are greatly needed.

This combination therapy had limited activity in this patient population. The reasons for this finding remain speculative. There did not appear to be a limitation of adequate drug dosing since the combination was well tolerated. Although the majority of patients were on known enzyme-inducing anti-epileptic agents at the time of treatment, there is no documented interaction with etoposide or tamoxifen that would suggest increased clearance or lower than expected serum concentrations of the agents. The most likely reason is that at this point of salvage therapy, the tumor cells probably consist of a highly resistant population that escapes the potential synergistic effect of the combination.

Table 4. Histology of patients with stable disease or response.

CR	1 anaplastic astrocytoma
PR	2 glioblastoma multiforme 1 low-grade mixed glioma
SD	4 glioblastoma multiforme 1 anaplastic astrocytoma 1 anaplastic mixed glioma 1 low-grade mixed glioma

CR: Complete response; PR: Partial response; SD: Stable disease.

Highlights

- This trial evaluated the combination of high-dose tamoxifen and etoposide in patients with both high- and low-grade glioma that was refractory to radiation therapy and prior chemotherapy regimens.
- Of 39 evaluable patients, there was one complete response, three partial responses and seven stabilizations of disease.
- Total response rate was 27%.
- Median time to tumor progression was 2 months and median survival was 5 months.
- Six-month progression-free survival was 10%.
- Results from analyses including and excluding the patients with low-grade glioma did not differ significantly.
- Comparisons with previously described studies in patients with malignant glioma are difficult, as most studies exclude patients with an initial diagnosis of low-grade glioma.
- It is encouraging that activity was seen in patients with very refractory tumors and this regimen represents a potential salvage treatment for patients with recurrent glioma.

Conclusion

The combination of high-dose tamoxifen and oral etoposide was well tolerated but had limited efficacy in this group of heavily pretreated patients. Nevertheless, it is encouraging that there was observed activity in patients with very refractory tumors and this regimen represents a potential salvage treatment for patients with recurrent glioma.

Acknowledgements

This study was supported by NIH/NCI grant PO1 CA13525. The authors thank Sharon Reynolds, Department of Neurological Surgery, University of California San Francisco, CA, USA, for editorial support.

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