Salvage Chemotherapy With Tamoxifen for Recurrent Anaplastic Astrocytomas

Marc C. Chamberlain, MD; Patty A. Kormanik, RN, CNP

Background: A prospective phase 2 study of daily oral tamoxifen citrate in young adults with recurrent anaplastic astrocytomas.

Methods: Twenty-four patients (15 men; 9 women) aged 19 to 45 years (median age, 31.5 years) with recurrent anaplastic astrocytomas were treated. All patients had been treated previously with surgery and involved-field radiotherapy (median dose, 60 Gy; range, 59-61 Gy). In addition, 22 patients were treated adjuvantly with nitrosourea-based chemotherapy (combined procarbazine hydrochloride, lomustine, and vincristine sulfate in 16; carmustine in 6). All patients were treated with salvage chemotherapy at first recurrence, with 1 to 4 chemotherapy regimens (median, 1 regimen). Tamoxifen citrate was administered orally at a fixed dosage of 80 mg/m² as a single or a twice-daily dosage. Neurologic and neuroradiographic evaluation were performed every 12 weeks, operationally defined as a single cycle of tamoxifen.

Results: All patients were able to undergo evaluation. A median of 4 cycles of tamoxifen (range, 1-8 cycles) were administered. No tamoxifen-related toxic effects were seen, nor were there any treatment-related deaths. Four patients (17%) demonstrated a neuroradiographic partial response; 11 patients (46%), stable disease; and 9 patients (38%), progressive disease following a single cycle of tamoxifen. Time to tumor progression ranged from 3 to 25 months (median, 12 months). Survival ranged from 3 to 27 months (median, 13 months). Five patients are alive, with 3 receiving alternative chemotherapy regimens and 2 continuing to receive tamoxifen. In the group with responding and stable disease, median survival was 15 months (range, 8-27 months).

Conclusion: Tamoxifen demonstrated modest efficacy with no apparent toxic effects in this heavily pretreated cohort of young adults with recurrent anaplastic astrocytomas.

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PATIENTS AND METHODS

ELIGIBILITY CRITERIA

Patients must have undergone previous surgery and had a recurrent neuropathologically proven anaplastic astrocytoma. Patient ages could range from 18 to 50 years. Tumors must have progressed following definitive radiotherapy and at least 1 previous chemotherapy regimen that included a nitrosourea. At least 4 weeks must have elapsed since the last dose of chemotherapy (6 weeks for nitrosoureas), and patients must have recovered from the adverse effects of previous therapy. Patients could not have received previous tamoxifen therapy. Patients must have had radiographically measurable intracranial disease wherein recurrent tumor was bidimensionally measurable using radiography (cranial contrast-enhanced magnetic resonance imaging [MRI] or computed tomography [CT]).

Reoperation for confirmation of recurrent anaplastic astrocytomas was not required. Pregnant or lactating women were not permitted to participate. Patients of childbearing potential age implemented adequate contraceptive measures during participation. Patients must have had an Eastern Cooperative Oncology Group performance status of 0 to 2 (Karnofsky score ≥60) and a life expectancy greater than 3 months.

Adequate hematologic, renal, and hepatic functions were required and were defined by the following: absolute granulocyte count of at least 1.5 × 10⁹/L or white blood cell count of at least 4.0 × 10⁹/L; platelet count of at least 100 × 10⁹/L; total bilirubin level of no more than 30.8 μmol/L (1.8 mg/dL); transaminase level of no more than 3 times the upper limit of normal; creatinine concentration of no more than 137.2 μmol/L (1.8 mg/dL); and normal results of an electrocardiogram.

All patients were aware of the neoplastic nature of their disease and willingly consented to participate after being informed of the procedures to be used, experimental nature of the therapy, alternatives, potential benefits, side effects, risk, and discomforts. Patients with meningeal gliomatosis were not eligible. No serious concurrent medical illnesses or active infection could be present that would jeopardize the ability of the patient to receive tamoxifen therapy. Patients could not have active concomitant malignant disease except skin cancer (squamous cell or basal cell).

IMAGING

Cranial CT was performed on a commercially available scanner (GE 9800; General Electric, Milwaukee, Wis). Contiguous 10-mm-thick axial sections were obtained from the foramen magnum to the vertex before and after intravenous administration of iodinated contrast media (Conray 43; Mallinckrodt, Inc, St Louis, Mo). All postcontrast CT images were obtained within 20 minutes of iodinated contrast media infusion.

Cranial MRI was performed on a 1.5-T superconducting magnet (Signa; General Electric). Using a spin-echo pulse sequence, axial T₁ - (repetition time [TR], 3000 milliseconds; echo time [TE], 80 milliseconds) and proton density-weighted (TR, 3000 milliseconds; TE, 30 milliseconds) images were initially acquired. Subsequently, sagittal axial and coronal T₁-weighted (TR, 600 milliseconds; TE, 23 milliseconds) 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 dimeglumine (Berlex Laboratories, Cedar Knolls, NJ), coronal, axial, and sagittal T₁-weighted sequences (TR, 600

RESULTS

STUDY POPULATION

Twenty-four patients (15 men; 9 women) aged 19 to 45 years (median age, 31.5 years), with recurrent anaplastic astrocytoma (Table) were treated with tamoxifen. Recurrent anaplastic astrocytomas were defined by objective neuroradiographic progression (≥25% increase in tumor size) compared with previous neuroradiographic images using the criteria reported by Macdonald et al.

Patients presented at the time of tumor recurrence with the following signs and symptoms: increasing headache (n = 13), worsening seizures (n = 14), progressive hemiparesis (n = 7), new-onset homonymous hemianopsia (n = 3), and gait ataxia (n = 1). Patient performance status using the Karnofsky scale ranged from 70 to 100 (median, 90) at the time of neuroradiographically documented tumor recurrence and initiation of tamoxifen therapy. All patients had undergone previous subtotal resection of tumor. Tumor locations, including multicentric tumors, were as follows: frontal lobe (n = 9), temporal lobe (n = 3), occipital lobe (n = 4), parietal lobe (n = 7), thalamus (n = 2), septum pellucidum (n = 1), and cerebellum (n = 1). Twenty-two patients had lobar tumors, and 2 patients had multicentric tumors each with 2 noncontiguous locations. Results of pathological examination (reviewed by a panel of 3 neuropathologists at University of California, San Diego) showed all tumors to be anaplastic astrocytomas.

All 24 patients had been treated previously with adjuvant limited-field radiotherapy (Table), and in all, conventional fractionated radiotherapy was used in which 1.8 to 2.0 Gy was administered daily, with a median dose of 60 Gy (range, 59-61 Gy).

All patients were treated previously with a nitrosourea-based chemotherapy. Twenty-two patients received adjuvant chemotherapy as follows: 16, procarbazine, lomustine, and vincristine sulfate (range, 1-7 cycles; median, 4.5 cycles); 6, carmustine (range, 3-6 cycles; median, 5 cycles). All patients were treated with salvage chemotherapy before the introduction of tamoxifen and received a range of 1 to 4 therapiest (median, 1) (Table). Patients received an average of 5 cycles of salvage chemotherapy (range, 2-23 cycles). Tamoxifen therapy was begun in all patients immediately following documentation of salvage-chemotherapy failure as demonstrated by neuroradiographic progression and, in 18 patients (80%), clinical disease progression.

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milled at 60 minutes; TE, 25 milliseconds) were obtained. All postcontrast images were obtained within 30 minutes of gadolinium infusion. Cranial contrast-enhanced CT and MR images were independently reviewed by a panel of 3 neuroradiologists.

**DRUG SCHEDULE**

Tamoxifen citrate (Nolvadex; Zeneca Pharmaceuticals, Wilmington, Del) was administered to all patients at an oral fixed dosage of 80 mg/m² per day. Patients elected to take tamoxifen as a single or twice-daily oral dosage. Concomitant dexamethasone therapy was permitted for control of neurologic signs and symptoms. Tamoxifen was administered continuously and daily, pending clinical neuroradiographic evaluation at 1 and 3 months and subsequently, as we shall indicate. Tamoxifen was administered regardless of white blood cell count, absolute granulocyte count, or platelet count. All toxic effects, including hematologic due to oral tamoxifen therapy, were rated according to the Cancer and Leukemia Group B expanded toxic effects criteria. 10

Oral dexamethasone was given concurrently in 17 patients, and dosage was increased in 8 patients with documented clinical and neuroradiographic progression. Dexamethasone dosage was decreased in 7 patients, and therapy was discontinued in 2 patients as patient clinical status permitted.

**METHOD OF EVALUATION**

Blood counts were obtained monthly, neurologic examination was performed monthly, and contrast-enhanced cranial MRI and CT were performed at 1 and 3 months and every 3 months thereafter. A single cycle of tamoxifen was defined operationally as 3 consecutive months of daily oral tamoxifen therapy.

Neuroradiographic response criteria as defined by MacDonald et al 12 were used. Complete response (CR) was defined as the disappearance of all enhancing or nonenhancing tumor on results of consecutive CT or MRI at least 1 month apart, with the patient neurologically stable or improved and without taking any corticosteroids. Partial response (PR) was defined as a reduction of at least 50% in the size of tumor on results of consecutive CT or MRI at least 1 month apart, with the corticosteroid dosage stable or decreased and the patient neurologically stable or improved. Progressive disease (PD) was defined as an increase of at least 5% or more in the size of tumor or any new tumor on results of CT or MRI, or the patient neurologically worse while receiving a stable or increased corticosteroid dosage. Stable disease (SD) was defined as all other situations.

In patients with PD, PR, or CR, 1 additional cycle of tamoxifen was administered, following which patients again underwent assessment. Tamoxifen therapy was continued until documentation of PD, at which time patients were removed from study and therapy was discontinued or alternative therapy was offered.

**STATISTICAL CONSIDERATIONS AND EXPERIMENTAL DESIGN**

The study design was that of a phase 2 prospective protocol. It was assumed, based on a review of the literature, that a maximum tolerated dosage of 160 mg/d of tamoxifen citrate had been established. At this dosage, 24 response-assessable patients were studied to allow estimation of the response rate with a maximum SE of 10%. The study was approved by the University of California, San Diego, Institutional Review Board, and consent for the study was obtained from all patients.
A number of prognostic variables affect survival in patients with malignant gliomas, including histologic characteristics of tumor, patient age, and patient performance status.1-6,33,34 Accordingly, we selected patients with malignant gliomas, including histologic findings of anaplastic astrocytoma tumor. In a seminal report on the outcome of patients with anaplastic astrocytoma, Prados et al35 concluded that these young patients with excellent performance status (median Karnofsky performance status of 90) and histologically young patients with favorable prognostic features, in particular relapse at the time of first tumor recurrence were treated with a variety of salvage chemotherapy protocol regimens before initiation of tamoxifen therapy. Therefore, tamoxifen therapy was begun after at least 2 chemotherapy regimens, adjuvant nitrosourea-based chemotherapy following cytoreductive surgery and involved-field radiotherapy.

Despite the favorable group of patients selected for inclusion in our study, all patients underwent heavy pretreatment. As has become standard for patients with malignant gliomas, most patients (92%) were offered adjuvant nitrosourea-based chemotherapy following cytoreductive surgery and involved-field radiotherapy, surgery had failed. No patient was believed to be a candidate for reoperation or stereotactic radiotherapy, and surgery had failed. No patient was believed to be a candidate for reoperation or stereotactic radiotherapy, and surgery had failed. No patient was believed to be a candidate for reoperation or stereotactic radiotherapy.

A range of tamoxifen dosages have been championed in various reports, but no published data exist re-

### Table: Salvage Therapy With Tamoxifen for Recurrent Anaplastic Astrocytomas

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Tumor Location</th>
<th>Surgery</th>
<th>Radiation Dose, Gy</th>
<th>Chemotherapy (No. of Cycles)</th>
<th>Previous Salvage Chemotherapy (No. of Cycles)</th>
<th>Tamoxifen Citrate</th>
<th>Salvage Therapy</th>
<th>No. of Cycles</th>
<th>Response/Duration, mo†</th>
<th>Survival, mo</th>
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<tbody>
<tr>
<td>1/F/25‡</td>
<td>L frontal</td>
<td>STR</td>
<td>60</td>
<td>Vincristine sulfate (1)</td>
<td>Paclitaxel (6), high-dose oral procarbazine hydrochloride (1)</td>
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<td>Vincristine (6)</td>
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<td>Alive§</td>
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<tr>
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<td>Alive§</td>
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</table>

*Indicates left; R, right; STR, subtotal resection; SD, stable disease; PD, progressive disease; and PR, partial response.
†Indicates time to tumor progression.
‡Indicates previously described.
§Indicates receiving tamoxifen.
||Indicates receiving alternate therapy.

**COMMENT**

A number of prognostic variables affect survival in patients with malignant gliomas, including histologic characteristics of tumor, patient age, and patient performance status.1-6,33,34 Accordingly, we selected patients with favorable prognostic features, in particular relapse at the time of first tumor recurrence were treated with a variety of salvage chemotherapy protocol regimens before initiation of tamoxifen therapy. Therefore, tamoxifen therapy was begun after at least 2 chemotherapy regimens, adjuvant radiotherapy, and surgery had failed. No patient was believed to be a candidate for reoperation or stereotactic radiotherapy, and surgery had failed. No patient was believed to be a candidate for reoperation or stereotactic radiotherapy.

A range of tamoxifen dosages have been championed in various reports, but no published data exist re-
garding a dose-response relationship. It has been shown in vitro that to block the proliferation of malignant glioma cell lines, concentrations several-fold higher than those typically obtained during the treatment of breast cancer are required. Five- to 10-µmol concentrations of tamoxifen per liter in vitro inhibits protein kinase C. These in vitro inhibitory levels are achievable in vivo with oral tamoxifen citrate dosages of 160 to 240 mg/d. The selection of a dosage of 80 mg/m² per day was based primarily on these findings and secondarily on issues of high-dose oral tamoxifen toxic effects.

The most commonly reported side effects of high-dose oral tamoxifen are the induction of hot flashes; deep venous thrombosis; nausea; neurotoxic effects as manifested by tremor, ataxia, and dizziness; and QT interval elongation on results of electrocardiography. Side effects of oral tamoxifen are dose dependent, wherein lower doses have a low incidence of side effects. As judged by the lack of toxic effects in our study at a dosage of 80 mg/m² per day (160-180 mg/d), a higher dosage of tamoxifen may have been appropriate and could be identified in a standard phase I dose escalation study in patients with recurrent malignant gliomas.

Two other criticisms aside from dose selection may be directed at our study. First, no attempt was made to administer a loading dose of tamoxifen. Therefore, antiglial proliferative effects of tamoxifen are correspondingly delayed until tissue levels of tamoxifen and its active metabolite n-desmethyltamoxifen (n-dMT) are achieved. Several groups have recently examined this approach and have demonstrated that cytostatic micromolar concentrations of tamoxifen could be achieved within several days following administration of tamoxifen dosages in the range of 200 to 1000 mg/d. Moreover, continued delivery of high-dose oral tamoxifen increases plasma concentrations of tamoxifen and n-dMT to levels of 5 to 10 µmol/L. Tamoxifen and n-dMT cross the blood-brain barrier and have been shown to accumulate intratumorally to therapeutically effective levels.

The second criticism of our study relates to the lack of performance of pharmacokinetic studies. Since tamoxifen and n-dMT are cytostatic agents, sustained tumor levels are necessary for optimal effect. To achieve maximal effect, serum levels in the range of 5 to 10 µmol of tamoxifen per liter should be realized. The failure of tamoxifen in one third of patients in our study may reflect insufficient serum and tissue levels of tamoxifen. Future studies of high-dose oral tamoxifen may address both of these issues by measuring serum levels during initiation of tamoxifen and on achieving steady-state concentrations. A flexible dosing schedule based on serum levels would appear more appropriate using the 5- to 10-µmol/L tamoxifen concentration as the therapeutic target serum levels.

A variety of response rates to high-dose oral tamoxifen in patients with recurrent malignant gliomas have been reported and on average are in the range of 25% to 35%. Confounding interpretation of these studies are the variable daily dosage of tamoxifen administered, differing tumor histological characteristics, frequent coadministration of chemotherapy, initiation of tamoxifen therapy immediately after completion of radiotherapy, and in general, a failure to obtain measurements of serum tamoxifen levels. The response rate in our study (17% PR; 46% SD), although modestly lower than previously reported, is not confounded by the above-mentioned difficulties of previous studies, save for the failure to assay serum levels of tamoxifen.

In conclusion, daily oral tamoxifen at a dosage of 80 mg/m² per day in this small cohort of heavily pretreated young adults with recurrent anaplastic astrocytomas is associated with modest activity and no observable clinical toxic effects. Future studies of tamoxifen in patients with malignant gliomas appear warranted, including combination therapies with vinca alkaloids, etoposide, and platinum compounds. Combination therapy with vinca alkaloids or etoposide is based on tamoxifen interference with p-glycoprotein-dependent drug efflux, the major mechanism of drug resistance with these agents. Alternatively, combination therapy with platinum compounds enhances cellular responsiveness and increases in vitro tumor cytotoxic effects.

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REFERENCES


