A Phase I Study of High-Dose Tamoxifen for the Treatment of Refractory Malignant Gliomas of Childhood

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ABSTRACT

Recent studies have indicated that the proliferation of malignant gliomas is in part dependent on excessive activation of protein kinase C (PKC)-mediated pathways. Conversely, inhibiting PKC may provide a novel approach for blocking glioma growth. The antiestrogen tamoxifen, a moderately potent PKC inhibitor, has been shown in vitro to block the proliferation of malignant glioma cell lines at concentrations several-fold higher than those typically attained during the treatment of breast cancer; such serum concentrations may be achieved with doses > 40 mg/m² b.i.d. The safety and efficacy of these high doses for producing disease control in patients with malignant gliomas has recently been noted anecdotally, although a rigorous study of this agent has been lacking. To address this issue, we examined the safety and efficacy of high-dose tamoxifen in a series of children with malignant gliomas that had progressed after conventional therapy. An initial group was treated with 60 mg/m² p.o. b.i.d. and a second group with 100 mg/m² b.i.d. Steady-state serum tamoxifen and metabolite levels were measured in most patients. Toxicity with the regimen was minimal; two patients treated at the higher dose required reduction to the lower dose because of asymptomatic prolongation of the QT interval on an electrocardiogram. Although none of the patients exhibited clear-cut tumor regression, 4 of 14 patients had stabilization of previously progressive disease for at least 3 months; the longest survivor lived for 17 months after beginning tamoxifen. The moderate efficacy of this agent in otherwise end-stage disease coupled with its low toxicity and the relative ease of oral administration provides a rationale for proceeding with larger studies of this agent in patients with malignant gliomas, possibly as a means for potentiating the effects of conventional chemotherapeutic agents, which to date have shown limited efficacy in the treatment of these tumors.

INTRODUCTION

The outlook for children with malignant glial tumors is generally grim (1). Despite the use of aggressive radiotherapeutic and chemotherapeutic intervention, median progression-free survival is less than 18 months for supratentorial malignant gliomas that are not amenable to radical resection (2–4). The prognosis for patients with malignant gliomas of the brainstem is even worse, because significant surgical cytoreduction is rarely if ever feasible (5–7). Attempts to enhance disease control with high-dose hyperfractionated radiotherapy have been disappointing (5), as have efforts to achieve preradiation disease regression using a variety of conventional chemotherapy regimens, which have generally produced responses in fewer than 10% of children (summarized in Ref. 7). After recurrence of a malignant glioma, few children experience long-term survival despite additional conventional therapy, unless radical surgical cytoreduction is feasible. For patients with recurrent brainstem gliomas, almost 90% of children are dead within 9 months of initial recurrence (7).

Taken together, these discouraging results provide a strong impetus for exploring novel therapeutic strategies for tumor growth inhibition. In this context, recent studies from our laboratory (8–10) and elsewhere (11–15) indicate that the proliferation of malignant glioma cells may, in part, result from excessive activation of PKC-mediated pathways. Conversely, inhibition of PKC using a number of different agents has shown promise as a novel strategy for inhibiting the growth of malignant glial tumors in vitro and in vivo (8–10, 12–15). One such agent is the PKC-inhibiting triphenylethylene antiestrogen tamoxifen (9, 15), which, along with its metabolites, inhibits PKC activity. 

1. The abbreviations used are: PKC, protein kinase C; MRI, magnetic resonance imaging; EKG, electrocardiogram.
I I 10

These studies demonstrated a 25–35% frequency of disease escalation study of high-dose tamoxifen in children with recurrent disease (9, 13, 15). The profound in vitro effects achieved by this relatively well-tolerated (18–20) agent provided the basis for Phase I and II trials of tamoxifen in adult patients with gliomas that had progressed despite conventional treatment approaches (21–25). These studies demonstrated a 25–35% frequency of disease response or stabilization with minimal toxicity, even at the high doses needed to achieve tumor growth inhibition. Although encouraging, these preliminary studies failed to address a number of crucial issues, which formed the basis for the current study. First, patients were treated with a variety of doses of tamoxifen, in many cases below the range needed to optimally inhibit PKC, raising the question of whether the therapeutic effect of this agent had been exploited adequately. Moreover, data confirming that therapeutically effective levels of drug had been achieved were almost uniformly lacking. Secondly, tamoxifen was often administered shortly after radiotherapy or in conjunction with other chemotherapy, which complicated attempts to demonstrate an independent therapeutic effect of this drug. Finally, childhood malignant gliomas, which may differ in terms of their biological behavior from adult gliomas, were specifically excluded.

To address these issues, we embarked on a Phase I dose escalation study of high-dose tamoxifen in children with recurrent malignant gliomas after confirming that this agent had a striking inhibitory effect on the proliferation of pediatric gliomas in vitro (26). The two doses chosen for evaluation (60 and 100 mg/m² b.i.d.) were selected based on the expectation from prior studies (27) that they would yield serum levels of tamoxifen and metabolites in the range of 5–10 μM, which were shown to inhibit glioma proliferation in our previous in vitro studies (26). This study had two fundamental goals: (a) to examine the toxicity of escalating doses of tamoxifen in children and (b) to obtain a preliminary assessment of the steady-state levels of tamoxifen and metabolites achieved in this patient population. A secondary aim was to evaluate the efficacy of these high doses in controlling the growth of end-stage malignant gliomas. Herein, we report the results of this study, which indicate that tamoxifen is well tolerated at the high doses needed to achieve serum levels capable of inhibiting PKC and moderately effective in producing stabilization of otherwise progressive end-stage disease in children with malignant gliomas.

PATIENTS AND METHODS

Patient Eligibility and Study Entry Criteria. Children between the ages of 3 and 18 with malignant gliomas that had progressed after full doses of radiotherapy (≥5000 cGy) and other Phase II or III chemotherapy were eligible for inclusion in this study. For lesions outside the brainstem, histopathological examination of a biopsy or resection specimen obtained at initial diagnosis or progression must have demonstrated malignant glioma (anaplastic astrocytoma or glioblastoma multiforme), and progressive disease must have been demonstrable on computed tomography or MRI studies after treatment with conventional therapy. For lesions of the brainstem, the diagnosis was based on stringent clinical and imaging criteria, which included the presence of progressive cranial neuropathies and long tract signs in association with diffuse enlargement of the pons on MRI. Brainstem lesions that did not fulfill these criteria must have undergone biopsy and been found histologically to be malignant glioma before inclusion in this study. All such patients also had evidence of disease progression despite prior therapy.

At the time of study entry, patients were on no concurrent therapy with other antitumor agents except steroids. By protocol, at least 4 months must have elapsed since any prior radiotherapy and at least 4 weeks since completion of any previous chemotherapy. Patients must have had a life expectancy of at least 1 month and a Karnofsky performance score ≥60 or, for young children, a Lansky score (28) ≥60. Patients with evidence of ongoing infection were excluded. In addition, the following baseline laboratory values were required before study entry: (a) serum creatinine <2 mg/dl, serum urea nitrogen <30 mg/dl, and creatinine clearance ≥75% of normal; (b) liver function tests ≤3 times the upper limit of normal for aspartate aminotransferase, alanine aminotransferase, total bilirubin; (c) sodium, potassium, chloride, calcium, magnesium, phosphorus, and bicarbonate within normal limits; (d) neutrophil count >1000/mm³; (e) platelet count >100,000/mm³; and (f) prothrombin time and partial thromboplastin time within normal limits. Informed consent approved by the Institutional Review Board was obtained in each case.

Treatment Plan. Tamoxifen was administered p.o. on a daily basis. The first group of patients received a loading dose of 200 mg/m² on day 0, followed by a maintenance dose of 60 mg/m² b.i.d. A second group of patients was then treated with an initial loading dose of 300 mg/m² followed by a maintenance dose of 100 mg/m² b.i.d. Our plan was for at least six patients to be studied at each dose level, with dose escalations not carried out until at least six patients had completed 1 month of therapy at the previous dose level without severe (≥ grade 3) toxicity, as assessed by standard National Cancer Institute toxicity criteria. No dose escalations were carried out in the same patients. Tamoxifen therapy was to be discontinued entirely in patients with grade 4 toxicity to tamoxifen alone. In patients with grade 3 toxicity, tamoxifen was to be stopped and then resumed 2 weeks thereafter at the next lowest dose level (if applicable), at the discretion of the treating physician.

Response was graded at 6 weeks and 3 months using standard radiographic criteria, with stable disease corresponding to less than a 25% change in tumor volume with a stable clinical status on a stable steroid dose, regression corresponding to at least a 25% decrease in tumor volume, and progression corresponding to either a 25% or greater increase in tumor volume, the development of new lesions, the onset of clinical progression, or the need for increasing steroid doses to maintain clinical stability. Patients with objective response or stable disease were continued on tamoxifen for up to 1 year.

Required Observations during the Study. Follow-up clinical evaluations were performed 1 and 2 weeks, respectively, after starting tamoxifen treatment, then biweekly during tamoxifen therapy. A complete blood count, platelet count, electrolytes, blood urea nitrogen, creatinine and creatinine clearance, calcium, magnesium, phosphorus, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and urinalysis were
repeated on a weekly basis for 2 weeks and biweekly thereafter while the patient was on tamoxifen therapy.

Before treatment was initiated, tumor size was evaluated thoroughly by MRI. The maximal diameter of the lesion was recorded in all three planes on the basis of both T2 signal abnormality and T1 contrast enhancement. MRI of the neuraxis and/or lumbar cerebrospinal fluid cytological examination was also required to identify dissemination of disease before study entry. A MRI examination of the head was repeated 6 and 12 weeks after commencing tamoxifen therapy, and at 3-month intervals thereafter. Interval studies were obtained in the event of neurological decline during the course of treatment. Because progression of disease may produce symptoms and signs that mimic those of neurotoxicity, every effort was made to identify whether new neurological findings were treatment or disease induced. Neurological deterioration that coincided with an otherwise progressive disease may produce symptoms and signs that have also been noted by Trump et al. (27), is unclear, it was felt by the investigators and their institutional cardiology consultants to be disease induced. Because high-dose tamoxifen has been reported to prolong the QT interval (27), a baseline and 12-lead EKG was obtained in all patients before commencing tamoxifen therapy. Follow-up EKGs were obtained 1, 4, and 12 weeks after beginning tamoxifen. If abnormalities were detected on these studies, a formal cardiological consultation was obtained.

Blood was drawn for measurement of serum tamoxifen and metabolite levels in the majority of patients included in this study. Where feasible, this was obtained at 1 day, 1 week, 3 weeks, 6 weeks, 12 weeks, and 6 months after starting tamoxifen. Analysis of tamoxifen and metabolite levels was performed by postcolumn photoactivation fluorescence detection by using coupled column high-performance liquid chromatography (29).

**RESULTS**

Fourteen patients were entered on the study, seven on dose level 1 and seven on dose level 2. The age, sex, location of these lesions, and prior therapy are summarized in Table 1. Twelve patients harbored diffuse intrinsic brainstem gliomas that had progressed after conventional external radiotherapy or hyperfractionated radiotherapy and, in nine cases, after at least one other chemotherapeutic regimen. Two patients had cerebral malignant gliomas that had progressed despite the use of radiotherapy. Phase III chemotherapy, and multiple Phase I or II chemotherapeutic regimens. Five children had radiological evidence of disease dissemination before study entry.

The toxicity of high-dose tamoxifen in these patients was limited. None of the children had significant nausea or vomiting, evidence of thrombophlebitis, or neurotoxicity that was not otherwise attributable to progressive tumor. However, two children (cases 8 and 11) who were treated with the higher tamoxifen dose had asymptomatic prolongation of the QT interval beyond the upper limits of normal on surveillance EKGs. Although the clinical significance of this finding, which has also been noted by Trump et al. (27), is unclear, it was felt by the investigators and their institutional cardiology consultants to be an indication for dose reduction. This EKG abnormality resolved after stopping the drug for 2 weeks and resuming therapy at a lower dose level.

Although none of the patients had objective tumor regression on MRI studies performed 6 and 12 weeks after study entry, four patients (cases 5, 7, 8, and 14) had stabilization of previously progressive disease for at least 3 months (Table 2). All of these patients ultimately died of progressive disease 5, 10, 17,
Table 2  Summary of response status and drug concentrations in patients included in the study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tamoxifen dose (mg b.i.d.)</th>
<th>Duration in study</th>
<th>Response status</th>
<th>Survival after study</th>
<th>Time of drug levels</th>
<th>4-OH-Tam (ng/ml)</th>
<th>DD-Tam (ng/ml)</th>
<th>ND-Tam (ng/ml)</th>
<th>Tam (ng/ml)</th>
<th>Metabolite Y (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>6 wk</td>
<td>PD</td>
<td>3 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>6 wk</td>
<td>PD</td>
<td>9 wk</td>
<td>4 wk</td>
<td>ND</td>
<td>319</td>
<td>871</td>
<td>519</td>
<td>201</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>6 wk</td>
<td>PD</td>
<td>10 wk</td>
<td>1 wk</td>
<td>ND</td>
<td>366</td>
<td>1473</td>
<td>239</td>
<td>435</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>6 wk</td>
<td>PD</td>
<td>6 wk</td>
<td>4 wk</td>
<td>ND</td>
<td>632</td>
<td>1412</td>
<td>254</td>
<td>569</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>3 mo</td>
<td>SD/PD</td>
<td>10 mo</td>
<td>1 day</td>
<td>3.8</td>
<td>ND</td>
<td>293</td>
<td>455</td>
<td>19.8</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>6 wk</td>
<td>PD</td>
<td>10 wk</td>
<td>1 day</td>
<td>10.5</td>
<td>ND</td>
<td>262</td>
<td>357</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>3 mo</td>
<td>SD/PD</td>
<td>5 mo</td>
<td>1 wk</td>
<td>11.7</td>
<td>87.2</td>
<td>1133</td>
<td>695</td>
<td>140</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>11 mo</td>
<td>SD/PD</td>
<td>17 mo</td>
<td>1 day</td>
<td>26.8</td>
<td>1181</td>
<td>1367</td>
<td>304</td>
<td>1813</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>6 wk</td>
<td>PD</td>
<td>5.5 mo</td>
<td>1 day</td>
<td>27.9</td>
<td>684</td>
<td>1699</td>
<td>1487</td>
<td>1813</td>
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<tr>
<td>10</td>
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<td>8 wk</td>
<td>PD</td>
<td>14 wk</td>
<td>1 day</td>
<td>34.0</td>
<td>1051</td>
<td>1755</td>
<td>1218</td>
<td>1451</td>
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<tr>
<td>11</td>
<td>100</td>
<td>6 wk</td>
<td>PD</td>
<td>6 mo</td>
<td>1 day</td>
<td>33.7</td>
<td>721</td>
<td>1646</td>
<td>1235</td>
<td>1016</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>3 wk</td>
<td>PD</td>
<td>5 wk</td>
<td>1 day</td>
<td>42.8</td>
<td>1088</td>
<td>1637</td>
<td>1048</td>
<td>967</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>5 wk</td>
<td>PD</td>
<td>5 mo</td>
<td>1 day</td>
<td>47.2</td>
<td>801</td>
<td>2038</td>
<td>750</td>
<td>927</td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>6 mo</td>
<td>SD/PD</td>
<td>8 mo</td>
<td>1 day</td>
<td>30.0</td>
<td>872</td>
<td>2552</td>
<td>1075</td>
<td>941</td>
</tr>
</tbody>
</table>

PD, progressive disease; SD, stable disease; SD/PD, stable disease that subsequently progressed; 4-OH-Tam, 4-hydroxytamoxifen; DD-Tam, didesmethyltamoxifen; ND-Tam, N-desmethyltamoxifen; Tam, tamoxifen; Metabolite Y, tamoxifenol; ND, not detectable; NA, specimen not available for analysis.

and 8 months, respectively, after study entry. The other 12 children, including all five with disease dissemination at study entry, failed to respond to tamoxifen. All died within 6 months of study entry, in keeping with the known dismal prognosis in patients with progressive malignant gliomas. In 11 of the 12 patients who exhibited disease progression within 3 months of beginning tamoxifen therapy, no additional therapy was pursued (reinforcing the fact that these children were viewed as having "end-stage" disease at study entry); 1 child was treated with navelbine without response.

In reviewing the measurements of tamoxifen and metabolite levels (Table 2), it was apparent that steady-state levels of tamoxifen and N-desmethyltamoxifen were generally reached within 1 week after starting therapy; however, didesmethyltamoxifen levels often rose substantially between the 1st and the 2nd to 4th weeks. There was an expected trend toward higher levels among patients receiving the 100 mg/m² dose as compared to those receiving only 60 mg/m². However, because of the substantial variability in these levels between patients within a given dose level, these differences did not reach statistical significance. For example, mean serum levels of tamoxifen 2–4 weeks after starting therapy in the 60 mg/m² and the 100 mg/m² groups were 574 ± 298 ng/ml and 895 ± 471 ng/ml, respectively (0.05 < P < 0.1; Student’s t test). Levels of tamoxifen and its major active metabolites (didesmethyltamoxifen and N-desmethyl tamoxifen) were 2125 ± 598 and 2692 ± 1380, respectively (P > 0.1; Student’s t test). It is of interest in correlating the clinical responses with the serum levels of tamoxifen and its metabolites that the child who experienced the longest period of stable disease after beginning tamoxifen ther-
apy also had the highest levels of tamoxifen and metabolites measured in the study population. After the 1st week of therapy, these levels consistently exceeded 10 μM, the concentration at which nearly complete inhibition of glioma proliferation was noted in prior in vitro studies (26).

Two of the four patients who experienced stable disease after 3 months of tamoxifen were begun on combination therapy with courses of carboplatin (400 mg/m²/day for 2 days) and etoposide (100 mg/m²/day for 5 days) every 3 weeks in addition to tamoxifen in the hope of inducing objective tumor regression. The other two patients continued on tamoxifen alone. In the two children who received carboplatin and etoposide, the addition of these agents was tolerated without excessive toxicity. However, this combination failed to produce objective disease regression. One child (case 14) progressed after two courses of combination therapy; in the other (case 8), carboplatin and etoposide were discontinued subsequently after the seventh course at the family’s request, and the patient maintained stable disease while receiving tamoxifen alone for several additional months.

DISCUSSION

The rationale for examining the efficacy of tamoxifen as an antiproliferative agent for glial tumors was based on three observations: (a) prior studies had indicated that PKC, a family of serine-threonine kinases involved in growth factor-mediated signal transduction (30), appeared to be involved in regulating the proliferation of malignant glioma cells in vitro (8–15); (b) tamoxifen was known to be an inhibitor of PKC (16, 17); and (c) this agent had long been in widespread use for the treatment of breast cancer with an acceptable level of toxicity (18–20). Studies in our laboratory and elsewhere with tamoxifen in a series of established and low-passage cell lines derived from adult (9, 13) and pediatric (26) malignant gliomas indicated that proliferation was inhibited in a dose-dependent fashion by an estrogen receptor-independent mechanism. It was presumed that the antiproliferative effects of tamoxifen resulted in part from inhibition of PKC, because the median effective dose noted for tamoxifen-induced inhibition of proliferation in these in vitro studies was in keeping with the median inhibitory concentration for tamoxifen on glioma PKC activity (13). However, these observations do not exclude the possibility that tamoxifen also may be inhibiting other signaling pathways (31) that contribute to glioma proliferation and viability.

A caveat in translating the aforementioned in vitro results to the clinical setting is that the inhibitory effects of this agent on PKC activity and glioma proliferation were achieved at concentrations several-fold higher than those attained with doses typically used to treat breast carcinoma (i.e., 10–20 mg p.o. b.i.d.). These “conventional” doses only achieve serum tamoxifen concentrations in the range of 100–1000 ng/ml (approximately 0.3–3 μM; Refs. 32–34), whereas optimal inhibition of PKC activity and glioma growth requires concentrations of at least 3–10 μM. The safety and efficacy of administering substantially higher doses of tamoxifen has recently been examined by several groups (27, 35, 36). These studies demonstrated that micromolar concentrations of tamoxifen could be achieved within several days of administering doses in the range of 200–1000 mg/day. Moreover, continued delivery of high tamoxifen doses increased plasma concentrations of tamoxifen and N-desmethyltamoxifen, the principal metabolite of tamoxifen, to levels of 5–10 μM (27, 35). Like the parent drug, the principal tamoxifen metabolites not only are antiestrogenic but also inhibit PKC (15, 16), in some cases with greater potency than tamoxifen itself. Moreover, these compounds cross the blood-brain barrier (32, 34, 37) and, in a handful of patients with brain metastases (32, 37) and in a patient with a malignant glioma (22), have been shown to accumulate intratumorally to therapeutically effective levels.

In addition, recent studies have indicated that these high doses of tamoxifen can be administered for extended periods with a minimal increase in side effects compared to conventional doses. Millward et al. reported that tamoxifen doses in the range of 320 mg/day were well tolerated; toxicity consisted of severe nausea (5.8%) and thromboembolism (5.8%; Ref. 36). Comparable results were obtained by Stuart et al. using 480 and 720 mg/day of tamoxifen, although the incidence of nausea increased slightly and a number of patients reported mild subjective neurological symptoms, such as dizziness and unsteadiness of gait (35). Similarly, Trump et al. reported that short-term administration of tamoxifen doses of 150 mg/m² twice daily following a 400-mg/m² loading dose were generally well tolerated without significant toxicity (27). However, higher daily doses produced a progressive increase in the incidence of neurotoxicity consisting of tremor, hyperreflexia, dysmetria, gait ataxia, and dizziness; these effects were readily reversible following discontinuation of tamoxifen. Asymptomatic prolongation of the QT interval on EKG occurred at tamoxifen doses of 80 mg/m² or higher.

On the basis of these results, several studies have examined the safety and efficacy of high-dose tamoxifen in the treatment of adults with malignant gliomas that had progressed after conventional therapy. In a tamoxifen dose escalation study in adults, Vertosick et al. (23) noted a dose-dependent effect on postprogression survival time: doses in the range of 160–240 mg/day were well tolerated and produced a significant increase in the duration of survival in comparison to lower doses. Coul- dwell et al. reported a reduction or stabilization in tumor volume on serial computed tomography scans as well as clinical improvement in 4 of 11 patients with recurrent malignant gliomas treated with 160–200 mg/day of tamoxifen (22). In general, the treatment was well tolerated: deep venous thrombosis, nausea, and hot flushes were reported in one patient each. Recently, Preul et al. noted objective tumor biochemical responses to tamoxifen on magnetic resonance spectroscopic imaging in 7 of 14 patients with recurrent malignant gliomas (24). However, interpretation of the above studies was complicated by the lack of correllative measurements of serum tamoxifen levels and response data (to determine whether therapeutically effective concentrations of this agent had been achieved) and the fact that tamoxifen was in many cases administered shortly after or in conjunction with other adjuvant treatment approaches, which may have been partially responsible for the therapeutic effects observed. The present study provides a Phase I multicenter investigation of high-dose tamoxifen for the treatment of malignant gliomas that is unique in its use of rigorous entry criteria and its inclusion of children. In this study, 4 of 14 patients with previously progressive disease exhibited at least a 3-month
period of disease stabilization while on tamoxifen therapy. One child remained progression free for almost 1 year after study entry and survived for 17 months after beginning tamoxifen treatment. Although none of the patients exhibited obvious disease regression, this result was not unexpected, because tamoxifen is presumed to function predominantly as a cytostatic rather than a cytotoxic agent at the concentrations achieved in this study. Nonetheless, the potential for obtaining disease stabilization in what would otherwise have been considered end-stage situations is an encouraging observation. These modest results contrast with those of a prior anecdotal report of tamoxifen use in childhood brainstem gliomas. In that study, four of five children exhibited prolonged disease control (38); however, tamoxifen was administered in a variety of doses and, in some cases, shortly after radiotherapy, and at least one of the lesions was a low-grade glioma, making it difficult to determine the contribution of this agent to the outcome of children with malignant gliomas.

Although not indicative of an overwhelming therapeutic effect, the present results are superior to those achieved in children with recurrent brainstem gliomas using a variety of conventional chemotherapeutic agents, such as carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, procarbazine, and thiopeta, and the “eight drugs in 1 day” regimen (7), with substantially less toxicity. As such, our findings provide a realistic basis for proceeding with further efforts to explore the efficacy of tamoxifen in the treatment of these tumors. In correlating the clinical responses with the serum levels of tamoxifen and its metabolites, it is of interest that the patient who experienced the longest period of stable disease after beginning tamoxifen therapy also had the highest drug levels in the study population. In this child, tamoxifen and metabolite levels exceeded 10 μM, the concentration at which nearly complete inhibition of glioma proliferation was noted in prior in vitro studies (26). In view of the substantial variability between patients in steady-state tamoxifen and metabolites levels, this observation raises the issue of whether therapeutic monitoring of serum drug levels should be included as a way of adjusting dosing parameters in future clinical studies.

Another factor to be considered in planning future studies of this agent is the timing of drug administration during the patient’s clinical course. Because the drug was well tolerated and could be delivered p.o. on a long-term maintenance basis in an outpatient setting, this cytostatic agent could be combined logically with other cytotoxic chemotherapeutic agents to enhance their therapeutic efficacy in “front-line” treatment protocols. In the current study, the combination of tamoxifen with carboplatin and etoposide, two agents that have been used together as initial pre- or postradiation therapy in pediatric neuro-oncology treatment protocols, was well tolerated in the two instances in which it was used. These two agents constitute rational choices for inclusion in a combination regimen with tamoxifen, because tamoxifen has shown promise in enhancing the efficacy of etoposide by interfering with P-glycoprotein-dependent drug efflux (27, 39) and in enhancing cellular responsiveness to platinum derivatives by P-glycoprotein-independent mechanisms (40). Interestingly, the two patients with stable disease at 3 months who continued with tamoxifen alone exhibited disease progression shortly thereafter, whereas the two who began carboplatin and etoposide in addition to tamoxifen remained progression-free for several additional months. However, it is impossible to exclude the possibility that the disease in these patients may have been inherently more indolent. For example, patient 8, who had the longest survival after beginning tamoxifen and had received carboplatin and etoposide, also had the longest time to progression after initial diagnosis and treatment. Clearly, additional study of this combination in a less heavily pretreated cohort will be needed to determine whether this regimen holds any meaningful promise for the treatment of malignant gliomas.

In summary, the results of the present study indicate that high-dose tamoxifen can be administered safely to children with recurrent malignant gliomas. With tamoxifen doses of 100 mg/m² b.i.d., steady-state serum levels of tamoxifen and metabolites in the range of 5–15 μM can be achieved.

ACKNOWLEDGMENTS

We acknowledge the assistance of Barbara Shultz in data collection.

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