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Thiotepa and etoposide treatment of recurrent malignant gliomas: phase I study

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Abstract *Purpose:* To determine: (1) the maximum tolerable dose (MTD) of thiotepa (TT) that can be administered with etoposide without stem cell support; (2) whether this regimen is active against recurrent malignant gliomas. *Background*: Although several chemotherapeutic agents show minor activity against recurrent brain tumors, there is no consensus about the most effective regimen. The alkylating agent TT has excellent central nervous system (CNS) penetration and is synergistic with the topoisomerase II inhibitor etoposide. *Design/Methods*: Fifteen patients with recurrent malignant gliomas (14 glioblastomas, 1 anaplastic astrocytoma) received intravenous etoposide 100 mg/m^2 on days 1, 2, and 3, and intravenous TT (40, 50, 60, or 70 mg/m^2) on day 2. All had received irradiation, and eight BCNU. Chemotherapy was repeated every 3–4 weeks, with stepwise TT dose increments of 10 mg/m^2, provided toxicity was less than grade III. *Results*: The major toxicity was dose-limiting leukopenia. The MTD of TT in cycle 1 was 60 mg/m^2. All patients died of progressive disease and none died of chemotherapy-related complications. *Conclusions*: The MTD of TT in this regimen for recurrent malignant gliomas is 60 mg/m^2. Higher doses of TT would require colony-stimulating factors or stem cell support.

Key words Thiotepa · Etoposide · Malignant glioma · Chemotherapy

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Introduction

Despite the increasing use of chemotherapy in the treatment of high-grade gliomas, the median survival for patients treated with a multidisciplinary approach is still less than 1 year [14]. Although the use of adjuvant chemotherapy (such as BCNU, procarbazine or hydroxyurea) has led to a statistically significant improvement in survival [6], treatment at recurrence may be more difficult and the tumor less likely to respond [13].

Poor results with standard chemotherapy, and the encouraging experience with high-dose thiotepa (TT) as well as other agents in children with primary brain tumors [7], led us to design this phase I study in adults. We sought to determine the maximum tolerated dose (MTD) of intravenous (IV) TT in combination with a constant dose of etoposide in adults with previously treated, recurrent malignant gliomas at doses that could be used without stem cell support. In addition we evaluated the response rate to this combination of agents.

Etoposide is a semisynthetic agent that interferes with the scission-reunion reaction of the enzyme topoisomerase II, leading to inhibition of cellular replication [20]. It has been found to be active against a variety of systemic malignancies as well as central nervous system (CNS) metastases of adenocarcinoma [2]. Although cerebrospinal fluid concentrations have been found to be less than 5% of those in the plasma after IV administration [3, 19], drug levels can be detected in glioblastomas [18]. As a single agent at conventional doses, etoposide yields response rates of up to 22% in previously treated recurrent malignant gliomas. High doses of etoposide with stem cell support have led to response rates in the range 0–75% in patients with malignant gliomas [15, 19, 21]. Myelosuppression is the major dose-limiting toxicity, but nausea, vomiting or allergic reactions are also common.

TT is a highly lipid-soluble alkylating agent that shows activity against solid tumor malignancies such as breast or bladder carcinoma [10, 16]. It binds to DNA, causing single- or double-stranded DNA breaks. The drug is me-

Table 1 Hematologic toxicity. Values are median nadir (range)

TT dose (mg/m^2)	WBC (per mm^3)	ANC (per mm^3)	PLT ($\times 10^3$ per mm^3)	Hb ($g/dl/10^3$)
40	4.4 (2.5–4.8)	3408 (3003–3604)	263 (79–301)	13.0 (12.8–14)
50	2.2 (2.0–3.4)	2300 (1625–2970)	163 (102–224)	12.0 (12.2–13.0)
60	2.8 (1.4–4.1)	1357 (1120–3024)	159 (60–138)	12.0 (10–14)
70	1.0[a]	280[a]	73[a]	10.9[a]

[a] Range not available as only one patient received this dose

tabolized to tepa, itself a potent alkylator, via the hepatic P450 system [17]. Previous studies [4, 12] have determined that 65 mg/m^2 is the MTD in patients with systemic malignancies treated with an IV regimen; the major dose-limiting toxicity is hematologic. Pharmacologic studies have shown CNS penetration of TT, with concentrations in the cerebrospinal fluid equivalent to those in the plasma within 3 h of IV administration [11]. In vitro, both agents have cytotoxic activity against CNS tumor cell lines such as medulloblastoma [8, 9].

Materials and methods

Patients aged 18–75 years with recurrent malignant brain tumors (glioblastoma or anaplastic astrocytoma) and Karnofsky performance $\geq$50% were eligible. Recurrence was defined as $>$25% increase in the cross-sectional area of the contrast-enhancing tumor on serial MRI or CT scans. All patients had adequate bone marrow function, defined by a white blood cell count (WBC) $>$4000 cells/mm^3, hemoglobin (Hb) $>$10 g/dl and platelet count (PLT) $>$150 000/mm^3, adequate liver function (bilirubin $<$1.5 mg/dl, normal transaminases), and normal renal function (creatinine $<$1.8 mg/dl and creatinine clearance $>$60 ml/min per 1.7 m^2 body surface area). Exclusion criteria was as follows: radiation therapy within 4 weeks and chemotherapy within 6 weeks of study entry, and pregnancy or lactation. Toxicity was graded according to NCI toxicity criteria. The treatment protocol was reviewed and approved by the Institutional Review Board of Columbia Presbyterian Medical Center. All patients signed an informed consent prior to enrollment into the treatment protocol.

Prior to treatment all patients underwent a complete physical and neurological examination, enhanced CT of the head or MRI and baseline complete blood count (CBC), coagulation profile, SMA-20, urinalysis, creatinine clearance, chest radiogram and electrocardiogram. CT or MRI were monitored every other cycle for tumor response. Tumor area was determined by measuring the tumor's largest dimension and multiplying by the perpendicular diameter. In determining response, corticosteroid dose must have remained stable over the intervening period. CBC and SMA-20 were monitored weekly. Standard response criteria were used: complete response (CR) was defined as disappearance of all tumor on CT/MRI for at least 4 weeks, partial response (PR) as $>$50% decrease in the area of the tumor, stable disease (SD) as no objective change, and progressive disease (PD) as increase in the tumor area by at least 25%.

Etoposide was administered IV at 100 mg/m^2 per day over 1–2 h on days 1, 2, and 3, and TT IV at 40–70 mg/m^2, on day 2 of each cycle. Cycles were repeated every 3–4 weeks. In the initial portion of the study, the dose of TT was escalated from 40 to 70 mg/m^2 in steps of 10 mg/m^2 in groups of three patients. Dose-limiting toxicity was evaluated for the first cycle and was defined as that dose of TT at which NCI grade III hematologic (or nonhematologic) toxicity occurred. Grade III hematologic toxicity was present if WBC was $\leq 1.9 \times 10^6/mm^3$, PLT $\leq$49 000/mm^3, or Hb $\leq$8 mg/dl. Prior to dose escalation in subsequent cycles, three patients must have tolerated the prior dose with toxicity less than grade III. If one of three patients in a group developed grade III toxicity, three additional patients had to tolerate the same dose level before dose escalation. In addition, to permit patients entered at lower dose levels to receive more dose-intense therapy in subsequent treatment cycles dose of TT for a given patient was increased provided toxicity was less than grade III. The MTD was defined as the highest dose tolerated by at least three patients. For grade III toxicity, chemotherapy was delayed for 1 week and started at 75% of the prior dose; for grade IV toxicity, TT dose was decreased by 50%.

Results

From June 1989 to June 1991, 15 patients were enrolled. There were 13 men and 2 women; the median age of the patients was 47 years (range 28–77 years). The tumor histology was glioblastoma multiforme in 12, anaplastic astrocytoma in 1; 2 patients had low-grade astrocytomas that recurred as glioblastoma multiforme. More than half of the patients had received prior nitrosourea chemotherapy as part of their initial treatment. The median number of BCNU cycles prior to treatment was two (range one to four), and the median dose of prior BCNU was 240 mg/m^2. At recurrence, six patients were treated with chemotherapy only, while eight patients first underwent surgical resection before entering the protocol. Of the 15 patients, 12 received two or more cycles of chemotherapy, while 3 received only one cycle. All patients had residual evaluable disease prior to protocol entry.

Four patients were treated at a TT dose of 40 mg/m^2, three at a dose of 50 mg/m^2, three at 60 mg/m^2, and one at 70 mg/m^2. We then treated four more patients at 60 mg/m^2 of TT. The dose-limiting toxicity was hematologic, with PLT and WBC being predominantly affected (Table 1). The maximal ANC (absolute neutrophic count) toxicity was grade IV, seen at doses of 70 mg/m^2. Likewise, the maximal grade of thrombocytopenia was grade II, seen at doses also of 60 and 70 mg/m^2. The median WBC nadir at a dose of 40 mg/m^2 was 4.4 mm^3, while the median WBC nadir at a dose of 70 mg/m^2 was 1.0. The median ANC nadir at a dose of 40 mg/m^2 was 3408 mm^3, while median ANC nadir for those patients receiving 60 mg/m^2 TT was 1357. Median PLT nadir at 40 mg/m^2 was 263000 mm^3, while the nadir at 70 mg/m^2 was 73000. The median time to nadir did not change with increasing doses of TT. The time to WBC nadir ranged from 12 to 15 days (median 14 days), for Hb nadir from 9 to 33 days (median 14.5 days) and for PLT nadir, from 11 to 15 days (median 14 days). To determine whether there was dose-cumulative toxicity we looked at the patients who had received multiple cycles of the same dose of chemotherapy and compared their median ANC, WBC, PLT and Hb during the first cycle of chemotherapy and during the second cycle. There was a mild, nonsignificant trend towards cumulative toxicity. No hepatic toxicity and no allergic reactions to etoposide were observed. One patient had *Pneumocystis carinii* pneumonia after cycle 1 of chemotherapy but recovered, and another had a nonfatal

intraventricular bleed, not associated with thrombocytopenia.

Although this was a phase I study, and the main aim was not to determine response to chemotherapy, 12 patients received more than one cycle of chemotherapy, and were considered evaluable for response. None of these 12 patients responded, yielding an upper 95% confidence limit of 22.1%. Two patients had SD lasting 2 months, but eventually progressed. Median time to progression from time of diagnosis was 48 days (range 28–120 days). Ten patients had PD without stabilization. Overall, all 15 patients died of disease; the median survival after recurrence was 4 months (range 2–7.6 months). No patient died of complications related to the chemotherapy regimen.

Discussion

For patients with recurrent malignant gliomas, most of whom have previously received nitrosourea chemotherapy, there is no accepted chemotherapy regimen with demonstrated efficacy. We chose to study TT because of its excellent CNS penetration, and added etoposide because of its synergy with alkylating agents. We sought to develop a regimen that could be given in the outpatient setting.

The first step was to determine the MTD for TT in this regimen, without stem cell support in a group of adult patients, many of whom had received prior nitrosourea treatment. The MTD in this patient population was 60 mg/m^2, similar to that found by Dwyer et al. in children with systemic malignancies [4] but higher than the 45 mg/m^2 found by Edwards et al. using TT as a single agent in patients with recurrent brain tumors [5].

There are relatively few studies using TT to treat primary CNS malignancies. Edwards et al. [5] found no responders in patients with recurrent gliomas treated with doses of 30 to 50 mg/m^2; one-third of the patients had stabilization of their disease. Heideman et al. [12] using 65 mg/m^2 in children with recurrent brain tumors reported a 23% response rate for medulloblastoma, but patients with glioblastomas did not respond. Regimens incorporating high doses of TT (up to 1200 mg/m^2) followed by autologous bone marrow support are promising as they produce responses of up to 60% in children with recurrent malignant brain tumors [1, 7].

The major toxicity of this regimen was hematologic, but in no instance was this toxicity life threatening. TT remains a promising drug for treatment of gliomas because of its excellent CNS penetration and potentially manageable hematologic toxicity. In view of the limited nonhematological toxicity, TT should be studied in future trials of adult primary brain tumors with further dose escalation and cytokine or stem cell support.

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