Phase I study of terameprocol in patients with recurrent high-grade glioma

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Terameprocol is a global transcription inhibitor that affects cell division apoptosis, drug resistance, hypoxia responsive genes, and radiation resistance in hypoxia. A multicenter, dose-escalation study was conducted in heavily pretreated patients with recurrent, measurable, high-grade gliomas. Terameprocol was administered intravenously for 5 consecutive days each month and discontinued for toxicity or progression. Patients taking enzyme-inducing antiseizure drugs (EIASDs) were escalated independently. Thirty-five patients with a median Karnofsky performance status of 80, median age of 46 years, and median of 2 prior treatment regimens were accrued. Doses of 750, 1100, 1700, and 2200 mg/day were administered. Terameprocol was reformulated to avoid acidosis related to the excipient and was well tolerated at 1700 mg/day. Hypoxia and interstitial nephritis were noted at 2200 mg/day. Concurrent administration of EIASD did not significantly affect the serum pharmacokinetics of the terameprocol. Although no responses were seen, stable disease was noted in 9 (28%) of 32 evaluable patients, with 5 (13%) continuing treatment for >6 months (≥6, 8, 10, 10, and ≥21 months). The overall median survival was 5.9 months. This phase I study defined the toxicity of terameprocol, determined that EIASDs do not affect its pharmacokinetics, and identified 1700 mg/day as the dose for future studies. Preclinical and human data suggest that terameprocol could be safely combined with radiation and temozolomide in newly diagnosed high-grade gliomas.

Keywords: glioblastoma, high grade glioma, phase I trial, terameprocol, transcription inhibitor.

Genuine progress has been made in the treatment of high-grade gliomas during the past decade. However, these cancers remain uniformly fatal, and to date, only surgery, radiation, and temozolomide have been conclusively shown to improve survival. Thus, testing of novel treatment approaches is critical to improving the outcome in patients with these malignancies.

Extracts and preparations from the creosote bush Larrea tridentata, found in the deserts of the southwestern United States and Mexico, have been ingested for generations by Native Americans to treat various medical disorders. Its leaves are used to make chamomile tea, which has been administered orally for cancer, venereal disease, tuberculosis, colds, and rheumatism. The active agent in the resin from the leaves is meso-teramoreprocol, determined that EIASDs do not affect its pharmacokinetics, and identified 1700 mg/day as the dose for future studies. Preclinical and human data suggest that this novel transcription inhibitor is worthy of further study. The long-term stability noted in some patients and the lack of associated myelosuppression suggest that terameprocol could be safely combined with radiation and temozolomide in newly diagnosed high-grade gliomas.

Keywords: glioblastoma, high grade glioma, phase I trial, terameprocol, transcription inhibitor.
Many of the medicinal effects of *L. tridentata* have been attributed to NDGA. Derivatives of this agent have been shown to inhibit the production of human immunodeficiency virus, herpes simplex virus, and human papillomavirus. In vitro, this appears to occur because of disruption of the activities of the Sp1 transcription factor.\textsuperscript{6–10} The meso-tetra-o-methyl nordihydroguaiaretic acid derivative (also known as terameprocol, EM1421, and M4N) retains this antiviral activity, induces reversible G2 cell-cycle arrest in mammalian cell lines without cytotoxicity, and is selectively tumoricidal in animal models of cancer (Fig. 1).\textsuperscript{8,11,12} The cell-cycle blockade appears to be related to the inhibition of the synthesis of cyclin-dependent kinase Cdc2 (also known as Cdk1, or p34), which is a primary regulator of the G2/M transition of the cell cycle.\textsuperscript{3,13,14}

Terameprocol also inhibits the production and activation of survivin. This Sp1 regulated protein is primarily present in tumor and fetal cells and is an inhibitor of apoptosis protein.\textsuperscript{14–16} Therefore, it prevents tumor cells from entering the caspase-induced cell-death pathway that would otherwise lead to their destruction.\textsuperscript{17} Terameprocol, through the Sp1 mechanism described above, prevents the transcription of the gene encoding survivin. Moreover, for survivin to be active, it must be phosphorylated by Cdc2. Because the production of Cdc2 is also reduced in the presence of terameprocol, survivin activation is substantially down-regulated. This mechanism of action is consistent with findings in animal cancer models in which terameprocol-treated tumor cells become apoptotic while surrounding healthy tissues, which do not rely on survivin, are not affected.\textsuperscript{11,12}

Terameprocol has been studied in humans with cancer. A phase I study of intral esional terameprocol in patients with recurrent and refractory head and neck cancer administered weekly injections each designed to deliver 20 mg of terameprocol per cubic centimeter of tumor.\textsuperscript{18} In 5 of the 6 patients who completed 3 doses of terameprocol, the tumor became necrotic without injury to adjacent tissues. Pharmacokinetic studies documented systemic absorption of the terameprocol, with peak plasma concentrations 2 h after these intratumoral injections. The local efficacy after intratumoral administration and documentation of systemic absorption without local or systemic toxicities prompted the development of systemic formulations. Escalating doses of intravenous terameprocol administered for 3 consecutive days each month were studied in patients with advanced systemic cancers.\textsuperscript{19} Metabolic acidosis was noted at a daily dose of 3300 mg, which was felt to be secondary to conversion of the excipient polyethylene glycol 300 (PEG 300) to oxalic acid. An additional phase I study of refractory solid tumors administered up to 4200 mg of terameprocol over a 24-h infusion period using a schedule of 1 dose day per week for 3 weeks, followed by 1 week of rest.\textsuperscript{20} Another study in patients with advanced hematologic malignancies found the maximum tolerated dose (MTD) to be 1500 mg 3 times weekly for 2 of every 3 weeks.\textsuperscript{21} A partial response was observed in each of the latter 2 studies. We report the results of a phase I study of terameprocol in patients with recurrent high-grade gliomas.

**Methods**

This study was conducted by the New Approaches to Brain Tumor Therapy CNS Consortium and funded by the National Cancer Institute (National Institutes of Health, CA-62475 New Approaches to Brain Tumor Therapy CNS Consortium, to P.I.G.). The clinical protocol was reviewed and approved by the Cancer Therapy Evaluation Program of the National Cancer Institute and by the institutional review board of each participating institution (Johns Hopkins University, Cleveland Clinic, University of Pennsylvania, Henry Ford Hospital, Massachusetts General Hospital, and the H. Lee Moffitt Cancer Center). Erimos Pharmaceuticals provided the terameprocol and compatible infusion tubing for the administration of this drug.

**Study Objectives**

The primary objective of this study was to determine the MTD of terameprocol administered as a daily intravenous infusion for 5 consecutive days every 28 days to adults with recurrent high-grade glioma. The secondary objectives were to (1) determine the effects of hepatic enzyme-inducing antiseizure drugs (EIASD) on the pharmacokinetics of this agent, (2) estimate the toxicity and tolerability associated with terameprocol, and (3) assess antitumor activity in terms of overall survival.
Patient Eligibility

Eligible patients were at least 18 years of age with histologically proven malignant glioma (anaplastic astrocytoma, anaplastic oligodendroglioma, or glioblastoma multiforme) progressive or recurrent after radiation with or without chemotherapy. Patients were required to have contrast-enhancing measurable disease by MRI or CT imaging and must have recovered from toxicities of prior therapy. An interval of at least 3 months must have elapsed since the completion of radiation therapy, 3 weeks since nonnitrosourea chemotherapy, and 6 weeks since nitrosourea chemotherapy. Normal hematologic, renal, and liver function was required, along with a Karnofsky performance status of ≥60%, a Mini Mental State Exam score of ≥15, and the ability to provide written informed consent. All patients with the potential for pregnancy or impregnating their partner had to agree to follow acceptable birth control methods, and women of childbearing potential were required to have a negative pregnancy test result. Patients were excluded if they had a serious concurrent medical illness, infection, or malignancy; if they had a known sensitivity to terameprocol, PEG 300, or medical illness, infection, or malignancy; if they had a required to have a negative pregnancy test result. Patients were excluded if they had a serious concurrent medical illness, infection, or malignancy; if they had a known sensitivity to terameprocol, PEG 300, or hydroxypropyl-β-cyclodextrin; or if they were pregnant, breast-feeding, or receiving other anticancer therapy for their brain tumor.

Treatment Plan

Eligible patients were assigned to 1 of 2 treatment groups (−EIASD or +EIASD) on the basis of their use of antiseizure drugs. Patients in the −EIASD group were either not being treated with an antiseizure drug or were taking one that does not significantly induce hepatic enzymes, such as gabapentin, lamotrigine, valproic acid, levetiracetam, tiagabine, topiramate, zonisamide, and felbamate. For purposes of this study, the +EIASD group included patients taking phenytoin, carbamazepine, phenobarbital, primidone, and oxcarbazepine. Inclusion in the −EIASD group required patients to discontinue using any +EIASD for at least 10 days. Drug doses in these 2 patient groups were escalated independently.

A standard phase I design was used with cohorts of 3 patients treated at each dose level and monitored for treatment-related toxicities. Escalation to the next dose proceeded in the absence of dose-limiting toxicities (DLTs). If a DLT occurred, an additional 3 patients were added at the same dose, and dose escalation continued if there were no DLTs in these patients. The MTD was considered to have been exceeded if >1 patient in a cohort (3–6 patients) experienced a DLT, thereby establishing the previous dose as the MTD. For purposes of this study, a DLT was defined as any of the following treatment-related adverse events occurring in the first cycle of therapy: (1) absolute neutrophil count ≤500 neutrophils/mm³, (2) platelet count ≤25 000 platelets/mm³, (3) febrile neutropenia, (4) any grade 3 or 4 nonhematologic toxicity, or (5) a delay in starting a subsequent course of treatment for >14 days because of incomplete recovery from toxicity.

The starting dose of terameprocol in both patient groups was 750 mg/day for 5 consecutive days each month by intravenous infusion. Further prespecified dose escalations were 1100, 1700, 2200, 3000, 4000, 5300, 7000, and 9300 mg/day. No intrapatient dose escalations were permitted. An analysis of the pharmacokinetic results was planned after accrual to the initial dose levels. If this revealed no significant EIASD effect on the pharmacokinetics of terameprocol, the use of separate +EIASD and −EIASD cohorts for dose escalation would be discontinued. Patients were considered to be evaluable for toxicity if they received 100% of the prescribed dose during their first month of treatment and were replaced if they withdrew before completing the first cycle for reasons other than toxicity. Treatment was continued until there was evidence of disease progression or unacceptable toxicity or the patient decided to discontinue treatment for any reason.

Drug Administration

The terameprocol dosing schedule was chosen on the basis of information and advice from Erimos Pharmaceuticals. Terameprocol was infused though a central or peripheral line at 150 mL/hour using a terameprocol-compatible infusion system provided by Erimos Pharmaceuticals. Antiemetics were not administered, and anticonvulsants and corticosteroids were administered as clinically indicated. If a patient developed a DLT, a subsequent dose of terameprocol could be administered after resolution of the toxicity by lowering the dose to the previous dose level. Failure to tolerate the lowest dose (750 mg/day) resulted in the patient being withdrawn from the study.

Because terameprocol is poorly soluble in water, it was formulated for intravenous administration as a 10 mg/mL solution in a vehicle composed of PEG 300, hydroxypropyl-β-cyclodextrin, and water for intravenous administration (designated as CPE). In previous clinical trials of this agent using the CPE formulation, patients frequently developed a reversible metabolic acidosis attributable to the metabolism of the PEG. As a result, during the conduct of this study, the formulation was changed to eliminate PEG. The new PEG-free formulation, referred to as TC6, contained terameprocol at a concentration of 6 mg/mL, hydroxypropyl-β-cyclodextrin, and water. With the conversion to the new formulation, one additional cohort of patients was added using TC6 formulation at the last terameprocol dose administered with CPE (Table 2).

Pharmacokinetic Studies

Blood samples for characterizing terameprocol pharmacokinetics were obtained from a peripheral vein before administration and at the following times after starting the first daily infusion: 0.25, 1.0, 1.25, 1.5, 2.0, 3.0,
4.0, 6.0, and 24 h. Blood was collected in tubes without an anticoagulant and permitted to clot for approximately 30 min before centrifuging (1200–1500 × g, 15 min, 4°C). The serum was removed and stored at −20°C until thawed for analysis by high performance liquid chromatography with tandem mass spectrometry by Covance Bioanalytical Services. The lower limit of quantitation of the analytical method was 10 ng/mL, for which the interday accuracy and precision were 98.8% and 3.5%, respectively. Serum concentration-time profiles of the drug for individual patients were fit to model-independent equations for continuous intravenous drug input with either bi- or triexponential first-order elimination by weighted nonlinear regression using WinNonlin Professional software, version 5.0 (Pharsight).22 Final values of the iterated parameters in the best-fit equation were used to calculate all pharmacokinetic variables according to standard equations.23 The paired 2-tailed t test was used to compare mean pharmacokinetic variables between the −EIASD and +EIASD treatment groups after logarithmic transformation of the data. P < .05 was the criterion for statistical significance.

Efficacy End Points

Tumor response and progression were categorized using the Macdonald criteria.24 Patients were defined as having progressive disease if there were (1) new lesions on serial neuroimaging studies, (2) >25% increase in the bidirectional measurement of contrast-enhancing tumor on MRI or CT, or (3) progressive neurologic abnormalities that could not be attributed to etiologies other than tumor progression. Overall survival was assessed using the Kaplan-Meier method.25 Patients who had not died prior to data cutoff were censored at the last date on which they were known to be alive.

Results

Patients

A total of 35 patients participated in this research study during 2007–2008. Sixteen (46%) of these patients were male, 32 were white, 2 were African American, and 1 was Asian. They had a median age of 46 years (range, 29–71 years) and a median Karnofsky performance status of 80 (range, 60–100) and had received a median of 2 prior chemotherapy regimens (range, 1–6). The last documented histologic diagnosis was glioblastoma in 15 patients (43%), anaplastic oligodendroglioma in 11 patients (31%), and anaplastic astrocytoma in 9 patients (26%).

Table 2. Observed toxicities with at least possible attribution to terameprocol as classified by the National Cancer Institute’s Common Toxicity Criteria (version 3.0)

<table>
<thead>
<tr>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Dermatology/skin</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td>15</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Neurology</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary/upper respiratory</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal/genitourinary</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood/bone marrow</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic/laboratory</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal/soft tissue</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac general</td>
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</table>

Toxicities and MTD

A summary of the total number of patients treated and the number of observed DLTs as a function of dose, formulation, and EIASD administration is presented in Table 1. A summary of observed toxicities is provided in Table 2. A total of 18 patients participated in the −EIASD cohort. Three patients were treated at doses of 750, 1100, and 1700 mg/day without DLT for 2, 3, and 23 months; 1, 2, and 10 months; and 2, 2, and 4 months, respectively. At 2200 mg, 1 of 3 patients developed a grade 3 ileus, and thus, another 3 patients were added to the cohort. One of these developed grade 3 dyspnea. These patients were treated for 1, 1, 1, 2, 2, and 4 months. Because 2 of 6 patients at the 2200 mg dose level had DLTs, the MTD with the PEG formulation was determined to be 1700 mg/day. After reformulation to a PEG-free infusion, 3 additional patients were treated at 1700 mg without DLTs for 2, 2, and 6 months.

A total of 14 patients participated in the +EIASD cohort. These patients were receiving phenytoin (10), carbamazepine (3), and oxcarbazepine (1). No DLTs were seen in 3 patients treated at 750 mg/day. These patients received 1, 2, and 8 months of treatment before developing progressive disease. Four patients were treated at a dose of 1100 mg/day, because 1 of the first 3 patients accrued was invaluable for the toxicity evaluation and was replaced. No DLTs were observed, and
Table 3. Characteristics of patients with long disease stability while receiving terameprocol treatment

<table>
<thead>
<tr>
<th>Months receiving terameprocol</th>
<th>Age</th>
<th>KPS</th>
<th>Histology</th>
<th># Prior Therapies</th>
<th>Years from initial cancer diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6+</td>
<td>46  F</td>
<td>90</td>
<td>Anapl Oligo</td>
<td>2</td>
<td>3 yrs</td>
</tr>
<tr>
<td>8</td>
<td>37  M</td>
<td>90</td>
<td>Anapl Astro</td>
<td>2</td>
<td>8 yrs</td>
</tr>
<tr>
<td>10</td>
<td>48  M</td>
<td>90</td>
<td>Anapl Astro</td>
<td>2</td>
<td>2 yrs</td>
</tr>
<tr>
<td>10</td>
<td>49  F</td>
<td>70</td>
<td>Anapl Oligo</td>
<td>3</td>
<td>7 yrs</td>
</tr>
<tr>
<td>21+</td>
<td>33  F</td>
<td>90</td>
<td>Anapl Oligo</td>
<td>1</td>
<td>8 yrs</td>
</tr>
</tbody>
</table>

Table 4. Comparison of overall mean pharmacokinetic parameters between the 2 treatment groups

| Parameter               | Treatment group | Difference (%) | P-value
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>+EIASD</td>
<td>-EIASD</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>18.2 ± 8.8</td>
<td>17.1 ± 9.4</td>
<td>6.4</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>53.7 ± 14.6</td>
<td>54.4 ± 20.8</td>
<td>1.3</td>
</tr>
<tr>
<td>$V_{ss}$ (L)</td>
<td>706 ± 425</td>
<td>612 ± 478</td>
<td>15.4</td>
</tr>
</tbody>
</table>

*aTwo-tailed t test of log transformed data assuming unequal variances.

Pharmacokinetics

Serum concentration-time data that were amenable to pharmacokinetic analysis for the initial daily dose of terameprocol were available for 9 patients in the +EIASD treatment group and 16 patients in EIASD group. The mean and standard deviation for the total body clearance, steady-state apparent volume of distribution, and terminal phase half-life of the drug in the 2 treatment groups are presented in Table 4. There were no differences between any of these parameters that approached statistical significance, suggesting that the concurrent administration of EIASD does not have a clinically significant effect on the serum pharmacokinetics of terameprocol.

Efficacy

No radiologic responses were observed after the administration of terameprocol. However, stable disease was noted in 9 (38%) of 32 evaluable patients. Five patients (13%) continued treatment for >6 months (6, 8, 10, 10, and 21+ months). As noted in Table 3, those who continued terameprocol treatment for >6 months were <50 years of age, with anaplastic (grade III) tumors and a long interval between diagnosis and terameprocol therapy. The median survival of patients in this study was 5.9 months.

Discussion

Terameprocol is a unique anticancer agent in many respects. NDGA has a long history of being safe in humans. It has been ingested for medicinal purposes by Native Americans for generations, used extensively as a preservative in American foods, and was the primary ingredient in skin creams used to treat sun-induced skin growths.3,13 In addition, there are abundant preclinical data attesting to its ability to inhibit the replication of Sp1-regulated viruses, such as human immunodeficiency virus and herpes simplex virus, and to target Sp1-regulated proteins that block progression of the cell cycle and regulate the expression of cell cycle genes, such as cyclin-dependent kinase I (CDK1 or CDC2), survivin, and vascular endothelial growth factor (VEGF).3,6–11,13–16,19,26–33 In addition, studies suggest that this agent could also be involved in MDR1-related drug resistance, HIF1-α–related radiation resistance, and the expression of SP1 regulated hypoxia genes, such as VEGF.3,13,34 Efficacy has been seen in prostate, colorectal, leukemia, and breast cancer cell lines and in human tumor xenografts of bladder, melanoma, colon, breast, and liver cancers.35–39 There has also been synergistic activity when terameprocol is combined with conventional cytotoxic chemotherapy agents.19,34

These studies provide ample justification to explore terameprocol as a relatively novel nontoxic anticancer agent. This drug has now been administered in patients intratumorally, intravaginally, and...
intravenously.  

Partial and complete responses were noted in patients with cervical intraepithelial neoplasia after the topical application of terameprocol, and intratumoral administration in patients with recurrent head and neck cancers resulted in necrosis and ulceration of the tumor within 2 weeks without systemic toxicity.  

A phase I trial of intravenous terameprocol was conducted in patients with treatment refractory solid tumors using a 30 min intravenous infusion for 5 consecutive days each month. Doses ranged from 100 to 3300 mg/day, and the recommended phase II dose on this schedule was 2200 mg/day.

This agent was selected for evaluation in high-grade gliomas because of its unique and diverse mechanisms of action, its low molecular weight and high lipid solubility, and its nonmyelosuppressive toxicity profile. The study reported in this article defines the toxicity profile in patients with recurrent high-grade gliomas. In addition, it determined that concomitant administration of EIASD does not affect the pharmacokinetics of terameprocol. It also identifies 1700 mg/day for 5 consecutive days each month as the recommended dose for the new non-PEG containing formulation to be used in future studies. Encouraging long-term stability was noted in some heavily pretreated recurrent gliomas in this phase I study. As expected, after the administration of the single agent terameprocol, better results were seen in the patients with anaplastic gliomas than in patients with rapidly recurring glioblastomas.

Given preclinical data suggesting that combining this agent with radiation and classical chemotherapy drugs are likely to be synergistic, further studies of combined therapy are needed. The safety data and the lack of myelosuppression reported in this article suggest that terameprocol could be safely combined with temozolomide and radiation in patients with newly diagnosed high-grade gliomas. Despite the high lipid solubility and low molecular weight of this agent, it would be helpful to have information on the concentration of terameprocol achieved in intracranial tumors after intravenous administration before proceeding with formal efficacy studies. In addition, preclinical testing of combination regimens should be conducted prior to initiating human toxicity and efficacy studies.

Conflict of interest statement. None declared.

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References


