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A phase I trial of arsenic trioxide chemoradiotherapy for infiltrating astrocytomas of childhood

Kenneth J. Cohen, Iris C. Gibbs, Paul G. Fisher, Robert J. Hayashi, Margaret E. Macy, and Lia Gore

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland (K.J.C.); Department of Radiation Oncology (I.C.G), Department of Neurology, Stanford University Medical Center, Palo Alto, California (P.G.F); Department of Pediatrics, Division of Hematology/Oncology, Washington University School of Medicine, St. Louis, Missouri (R.J.H.); University of Colorado Anschutz Medical Campus and Children's Hospital Colorado, Aurora, Colorado (M.E.M., L.G.)

Background. Arsenic trioxide (ATO) has demonstrated preclinical evidence of activity in the treatment of infiltrating astrocytomas.
Methods. We conducted a phase I trial of ATO given concomitantly with radiation therapy in children with newly diagnosed anaplastic astrocytoma, glioblastoma, or diffuse intrinsic pontine glioma. Eligible patients received a fixed daily dose of 0.15 mg/kg of ATO once a week, with each subsequent cohort of patients receiving an additional dose per week up to a planned frequency of ATO administration 5 days per week as tolerated. Twenty-four children were enrolled and 21 children were evaluable.
Results. ATO was well tolerated throughout the entire dose escalation, resulting in confirmation of safety when administered 5 days per week during irradiation.
Conclusions. The recommended dose of ATO during conventional irradiation is 0.15 mg/kg given on a daily basis with each fraction of radiation therapy administered.

Keywords: arsenic trioxide, astrocytoma, chemoradiotherapy, pediatrics.

The successful treatment of children with infiltrating astrocytomas remains a challenge. Despite improvements in neurosurgical technologies, radiation therapy, and chemotherapy, the long-term survival for children with anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) remains poor. Even more challenging has been the treatment of children with diffuse intrinsic pontine glioma (DIPG), from which, despite innumerable therapeutic strategies, almost all children die within 6 months to 2 years from initial diagnosis. The "standard of care" for children with AA and GBM remains chemoradiotherapy, often with an alkylating agent, generally followed by adjuvant chemotherapy. For most children with DIPG, radiation therapy following diagnosis provides a period of palliation, often with transient improvement in neurologic symptoms. All other efforts to influence the natural history of irradiated DIPG have been ineffective, as detailed in a number of recent reviews.[1,2]

Arsenic trioxide (ATO) in a partially purified form was first used therapeutically for leukemias and solid tumors in China based on the hypothesis that it could induce terminal differentiation in cells, thus limiting their malignant potential. Some antitumor activity was observed in these cancers, although formal scientific reports are not available.[3] ATO has been shown to be highly efficacious in the treatment of acute promyelocytic leukemia, with a consistent remission rate.[4–6] In a subsequent multi-institutional study, 34/40 relapsed patients achieved complete remission of promyelocytic leukemia on ATO using a dose schedule of 0.15 mg/kg/day for 25 days, with up to 5 cycles administered without major cumulative toxicity.[5,7] Similar findings were reported in the pediatric population in a phase I study of children with refractory leukemia. In that study, 85% of all subjects with acute promyelocytic leukemia achieved a morphologic complete response. No responses were observed in non–acute promyelocytic leukemia patients. The recommended dosage was 0.15 mg/kg/day owing to dose-limiting corrected QT

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Corresponding Author: Kenneth J. Cohen, MD, MBA, The Johns Hopkins University School of Medicine, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Bloomberg 11379, 1800 Orleans St, Baltimore, MD 21287 (kcohen@jhmi.edu).

(QTc) prolongation or pancreatitis at 0.2 mg/kg/day dosing.[8] ATO is approved by the Food and Drug Administration for the treatment of promyelocytic leukemia.

ATO in Brain Tumors

Investigators have detected ATO within brain tissue 2–6 h following oral administration,[9] and more significantly, a higher concentration of ATO accumulates in tumor than in normal brain tissue in humans.[10] ATO has demonstrated a potent antivascular effect in murine models. There is a selective destruction of tumor vasculature and near-complete blockage of blood flow by ATO, resulting in central necrosis of a large experimental animal tumor.[11] This suggests that while the peripheral well-oxygenated cells that are radiosensitive can be treated by radiation, the poorly perfused hypoxic portion of the tumor that is radioresistant could be treated by ATO.

In experiments with Meth-A tumor in mice, fractionated radiotherapy given with weekly doses of ATO within 1 h of radiotherapy showed a synergistic response for local tumor control and survival of the animals. There was a significant growth delay of tumors receiving the combination of radiotherapy and ATO (tumor growth delay, 33 days) compared with either treatment alone (tumor growth delay, 1–5 days). Studies with rodent 9L gliosarcoma transplanted into the rat brain also revealed significant survival prolongation of the animals treated with ATO and radiosurgery.[12] A single dose of ATO was given within 1 h following radiosurgery. Median survival times of untreated control and ATO-alone treated animals were 19 and 18 days, respectively. Median survival from radiosurgery alone was 38 days. Combined radiosurgery and ATO treatment almost doubled the median survival time to 73 days. These results suggest that in these animal models, there is significant radiosensitization by ATO. Investigators have studied the effect of ATO in vitro in human glioma cell lines.[13] ATO, as a single agent, inhibits cell proliferation of 6 different cell lines in a dose-dependent manner. G_2/M-induced arrest was noted in all ATO treated samples. Autophagy (programmed cell death type II), as opposed to apoptosis (programmed cell death type I), was noted. Caspase inhibitors did not affect cell death, supporting the notion of type II cell death. Importantly, these findings suggest that ATO has a direct impact on gliomas entirely independently of a radiation sensitization mechanism.

On the basis of these preclinical findings, a phase I study of ATO in combination with radiation therapy for children with newly diagnosed AA, GBM, and DIPG was undertaken, the results of which we report here.

Materials and Methods

Eligibility

Children ≥ 3 and < 22 years of age with newly diagnosed high-grade glioma (AA, GBM, or gliosarcoma) or with DIPG were enrolled after institutional informed consent was obtained. Patients were previously untreated, except for surgery, and had a Lansky or Karnofsky performance status ≥ 60 and adequate organ function. Histologic diagnosis was required for patients with AA, GBM, and gliosarcoma. Children with DIPG were not required to undergo histologic confirmation of diagnosis, provided that clinical and neuroradiographic findings were consistent with DIPG. Ineligible were children with second-degree heart block or an absolute QT interval > 500 ms in the presence of normal serum potassium and magnesium values, pregnant patients, and those being treated with amphotericin B.

Surgery/Pathology

Maximal safe surgical resection was recommended for all children with a diagnosis of AA, GBM, or gliosarcoma. Postoperative MRI was obtained within 24–48 h after surgery. Patients were eligible based on the institutional pathology diagnosis. Central pathologic review was not mandated on this trial.

Treatment

Chemoradiotherapy commenced within 42 days following diagnosis. Radiotherapy dosage was determined by the institutional radiation oncologist but was anticipated to last approximately 6 weeks in all cases. Doses ranged from 5400 to 5940 cGy, dependent on tumor type and location. A fixed dosage of ATO (Teva Pharmaceuticals) of 0.15 mg/kg/day was utilized throughout the study. Electrocardiograms were monitored at study entry and then weekly during treatment to evaluate for possible QT prolongation, a known side effect of ATO. Dose level 1 was delivered at a frequency of 1 dose of ATO/week. Dose level 2 was delivered at a frequency of 2 doses of ATO/week, and the planned dose escalation continued to dose level 5, delivered at a frequency of daily ATO on all weekdays of radiation therapy. No escalation above 0.15 mg/kg/day of ATO or at a frequency exceeding 5 doses/week was planned. Each dose of ATO was diluted in 100 mL of 5% dextrose solution or 0.9% sodium chloride injection administered as a 1-h intravenous infusion, usually preceding a planned daily dose of irradiation. *Pneumocystis jiroveci* pneumonia prophylaxis was not mandated during treatment. Patients were considered evaluable if they completed the planned doses of ATO and a 30-day period of observation following the completion of irradiation or if a dose-limiting toxicity (DLT) occurred during the period of ATO therapy precluding further study drug administration. Patients who progressed during chemoradiotherapy were not considered evaluable but were evaluated for toxicity. Patients were deemed off treatment upon progression of disease and/or the start of another treatment; if the constraints of the protocol proved detrimental to the patient's health; if the patient/caregiver refused further treatment; or if the patient experienced a DLT. Patients were deemed off study at the time of their death.

Statistical Methods

The primary objective of the study was to determine the maximum tolerated dose (MTD) of ATO given in conjunction with radiotherapy. A stepwise dose escalation design was employed with a starting dose of 0.15 mg/kg given once weekly to cohorts of 3 patients. If a DLT was experienced in 1 of the first 3 patients at a dose level, then 3 additional patients were enrolled at that same dose level. The MTD was defined as the dose at which 0–2 out of 6 patients experienced a DLT. The dose was not to be escalated above dose level 5, and patients were to receive ATO only on days when radiation was administered. Six subjects were treated at the highest tolerated dose level to further test the safety of that dose level. A secondary objective was to assess the toxicity of ATO when given in conjunction with radiation utilizing the Common Terminology Criteria for Adverse Events version 3.0 for determination of grade of severity for each adverse event. Monitoring adverse events occurred from the time of consent signing until 30 days following the completion of the last dose of ATO.

Results

Between November 2005 and September 2010, twenty-four subjects signed informed consent at 4 participating institutions. Accrual to the trial was delayed when ATO was purchased by Cephalon Oncology from Cell Therapeutics, such that the majority of the subjects enrolled were accrued between 2008 and 2010. Three subjects were inevaluable (superior vena cava clot prior to start of study drug, parental withdrawal after signing consent, and progressive disease during chemoradiotherapy on day 33 of treatment). Demographic information and presenting diagnosis for the remaining 21 evaluable subjects are detailed in Table 1.

Three evaluable subjects were accrued at dose levels 1 through 3. One subject at dose level 4 experienced a DLT of neutropenia, which resolved after 3 days, resulting in an additional enrollment of 3 subjects at dose level 4 with no further DLTs observed. Six subjects were enrolled at dose level 5 with no DLTs noted (Table 2). Two subjects received the majority of their ATO administration following the daily fraction of radiation therapy. The most common adverse events reported were nausea, vomiting, fatigue, headache, and anorexia, although often listed as unlikely related to ATO administration by investigators. Adverse events with a possible, probable, or definite relation to ATO were generally reversible with no treatment. Adverse events attributed to ATO administration are listed in Table 3.

Table 1. Demographic information ($N = 21$)

Characteristic	
Age, median	9 y (range 3–19)
Sex (M:F)	(11:10)
Diagnosis, *n*	
DIPG	12
AA	4
GBM	4
Secondary GBM	1
Race/ethnicity, *n*	
White/non-Hispanic	9
White/Hispanic	8
Black/non-Hispanic	2
Asian/non-Hispanic	2

Table 2. Dose escalation enrollment ($N = 21$)

Dose Level/Days per Week	*n* Patients	DLT Observed
1 = 0.15 mg/kg/dose 1× per wk	3	0
2 = 0.15 mg/kg/dose 2× per wk	3	0
3 = 0.15 mg/kg/dose 3× per week	3	0
4 = 0.15 mg/kg/dose 4× per week neutropenia	6	1 grade 4
5 = 0.15 mg/kg/dose 5× per week	6	0

Owing to the use of radiotherapy for all subjects on this trial, coupled with the opportunity for subjects to receive investigator-recommended adjuvant therapy beginning 30 days following the completion of ATO/radiotherapy, no formal response assessment was undertaken. Time to protocol-defined treatment ranged from 3 to 17 months from the start of chemoradiotherapy. All children died of their tumors from 2 to 33 months from the start of chemoradiotherapy. The median times, in months, from diagnosis to death were 10 (range 2–22), 9 (range 8–23), and 13 (range 11–33) for DIPG, AA, and GBM, respectively.

Discussion

There is a growing body of preclinical evidence supporting the activity of ATO in the treatment of infiltrating astrocytomas. Early reports demonstrated the antiproliferative effect of ATO on cell cycle progression.[14,15] Subsequently, preclinical studies have shown the augmented impact of arsenic when given with radiation therapy.[12,16,17] Numerous publications have addressed the possible mechanisms of ATO-induced cell death in malignant glioma cells.[13,18–24] Further studies on the benefit of chemoradiotherapy with ATO have demonstrated an enhanced induction of autophagy through inhibition of phosphoinositide-3 kinase/Akt and activation of extracellular signal-regulated kinase 1/2 signaling pathways.[16]

This study confirmed the safety and tolerability of ATO given at a dosage of 0.15 mg/kg/day when administered concomitantly with focal radiotherapy for the treatment of infiltrating astrocytomas in children. No significant cardiac toxicities were noted. The therapy was well tolerated with modest toxicities, many of which are commonly attributed to irradiation alone. The study was originally designed to allow for dose escalations above 0.15 mg/kg on each day of radiotherapy but was amended following the report by Fox et al[8]

Table 3. Cumulative toxicities assessed[a] ($N = 22$)

	Toxicity Grade				
Toxicity term	1	2	3	4	5
Nausea	11	2			
Vomiting	8	2	1		
Fatigue	7	1			
Headache	4				
Anorexia	3	1			
Abdominal pain	3				
Pruritus	3				
Constipation	2	1			
Lymphopenia	1	1	1		
Ataxia	1	1			
Rash	1	1			
Extrapyramidal/involuntary movement	2				
Hemiparesis		2			
Neurology–motor (gait)	1	1			
Neutropenia				1 (DLT)	
Alopecia	1				
Cushingoid appearance	1				
Fever	1				
Striae	1				
Diarrhea	1				
Infection			1		
Tinnitus		1			
Tachypnea	1				
Insomnia	1				
Hypertension	1				
Mucositis	1				
Prolonged QTc	1				
Neuropathy–sensory	1				
Hypokalemia			1		
Hypomagnesemia	1				
Cough	1				
Allergic reaction	1				
Leukopenia	1				
Flushing	1				
Cardiac–other (T-wave abnormality)	1				

[a]According to the Common Terminology Criteria for Adverse Events, version 3.0 for all findings with a possible, probably, or definite attribution to ATO administration in the 22 patients evaluable for toxicity.

that reported a recommended daily dose of 0.15 mg/kg of ATO due to dose-limiting QTc prolongation or pancreatitis when the dosage was raised to 0.2 mg/kg/day in children with leukemia. Whether a higher dose of ATO administered in this study would be more efficacious during chemoradiotherapy is unknown. Of note, pharmacokinetic determinations were not undertaken in this trial, although given the identical dose levels, they would not be anticipated to differ from the results reported by Fox et al.

An additional area of uncertainty relates to the optimal time of ATO infusion in relation to the administered dosage of therapeutic radiation. This study allowed for the administration of ATO either before or after planned daily radiation therapy in an effort to address the complexity of daily infusions and irradiation, particularly for children requiring anesthesia for daily radiation therapy. A report by Ning and Knox[25] published in 2006 suggested that, at least in their preclinical model, ATO administration was most effective at 0–4 h after radiation therapy.[25] A more recent in vitro study suggested that pretreatment with ATO prior to administration of temozolomide, bevacizumab, and ionizing radiation led to fewer cells in G_0, suggesting the potential to increase sensitivity to other chemotherapeutics and radiotherapy.[26] While not mandated by the study, ATO was administered in advance of the daily dose of therapeutic radiation in 19 of 21 subjects. There were insufficient numbers of subjects who received post–external beam radiotherapy ATO to draw any in vivo conclusions.

A number of recent studies provide some additional observations that may have future therapeutic relevance. A variety of preclinical studies have demonstrated that ATO has a direct inhibitory effect on cancer stem-like cells. Mechanisms of this inhibition of cancer stem-like cells include deregulation of Notch inhibition[27] and downregulation of Sox2.[6] Hints to possible combinatorial therapies have been published, including combination with inhibitors of tumor necrosis factor–related apoptosis-inducing ligand,[28] of heat-shock protein,[29] and of heme oxygenase-1.[30]

An additional observation, relevant to the management of patients with infiltrating astrocytomas, medulloblastoma, and other solid tumors, is the finding first reported by Kim et al[31] that ATO antagonizes the hedgehog pathway at the level of the Gli2 transcriptional effector.[31] Further reports[32,33] have substantiated this finding. These findings raise the possibility that for particular tumor types, such as Sonic hedgehog–driven medulloblastoma, the use of ATO chemoradiotherapy might provide more targeted treatment than other chemotherapeutics, such as vincristine, that have been traditionally used during chemoradiotherapy.

In conclusion, ATO administered daily during delivery of radiation therapy is well tolerated, with minimal side effects. Given the low toxicity, coupled with a growing body of evidence regarding the mechanism of ATO-induced cytotoxicity, ATO may be an ideal agent for further combinatorial radiotherapy in the treatment of infiltrating astrocytomas and other pediatric solid tumors.

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