

## Phase I and pharmacodynamic study of arsenic trioxide plus radiotherapy in patients with newly diagnosed glioblastoma

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### Abstract

**Background.** When arsenic trioxide (ATO) was combined with radiation for treatment of transplanted murine gliomas in the brain, tumor response improved with disrupted tumor blood flow and survival was significantly prolonged.

**Methods.** Total of 31 patients with newly diagnosed glioblastoma were accrued to a multi-institutional, NCI-funded, phase I study to determine the maximum tolerated dose (MTD) of ATO administered with radiation. Secondary objectives were survival and pharmacodynamic changes in perfusion on magnetic resonance imaging (MRI). Patients (unknown MGMT and IDH status) received ATO either once or twice weekly during radiation without concurrent or adjuvant temozolomide.

**Results.** Median age: 54.9 years, male: 68%, KPS  $\geq$  90: 77%, debulking surgery: 77%. Treatments were well-tolerated: 81% of patients received all the planned ATO doses. Dose-limiting toxicities included elevated liver function tests, hypokalemia, and edema. The MTD on the weekly schedule was 0.4 mg/kg and on the biweekly was 0.3 mg/kg. The median survival (mOS) for all patients was 17.7 months. Survival on the biweekly schedule (22.8 months) was longer than on the weekly schedule (12.1 months) ( $P = .039$ ) as was progression-free survival ( $P = .004$ ). Similarly, cerebral blood flow was significantly reduced in patients treated on the biweekly schedule ( $P = .007$ ).

**Conclusions.** ATO with standard radiation is well tolerated in patients with newly diagnosed glioblastoma. Even without temozolomide or adjuvant therapy, the overall survival of all patients (17.7 months) and especially patients who received biweekly ATO (22.8 months) is surprising and accompanied by pharmacodynamic changes on MRI. Further studies of this regimen are warranted.

### Key Points

- Arsenic combined with radiation therapy is safe for patients with newly diagnosed glioblastoma and caused decreased tumor blood flow.
- Overall and progression-free survival prolonged especially in the twice weekly arsenic treatment arm than the weekly arm.

Following the first report of arsenic trioxide (ATO)-induced complete remission in patients with relapsed acute promyelocytic leukemia,<sup>1</sup> ATO therapy has become integral to the treatment

of patients with this disease.<sup>2,3</sup> Relapsed and newly diagnosed acute promyelocytic leukemias were successfully treated with low doses of 0.15 mg/kg of ATO per day in repeated cycles

## Importance of the Study

This translational study showed that arsenic combined with radiotherapy is safe and well tolerated in patients with newly diagnosed glioblastoma. Despite of the unknown MGMT and IDH status of the study patients, overall survival and progression-free survival time significantly prolonged especially in patients who received the twice weekly arsenic treatment arm than the weekly

arm without use of temozolomide. The prolonged survival time was correlated with reduced tumor blood flow. The result of improved survival warrants that arsenic with radiation should be evaluated for treatment of wild type IDH and/or MGMT unmethylated glioblastomas where temozolomide has limited activity.

without major cumulative toxicity. ATO showed multiple mechanisms through which it impaired signal transduction and produced various cellular effects including enhanced apoptosis, growth inhibition, promotion or inhibition of differentiation, and inhibition of mitochondrial respiratory function in leukemia cells.<sup>4-8</sup> Similar therapeutic effects of ATO have also been observed in other malignant cells including glioma cells. In preclinical studies with glioma cells, ATO was shown to induce apoptosis, autophagy and oxidative damage in glioma tumor-spheres,<sup>9</sup> and targeting glioma stem cells,<sup>10</sup> especially when ATO was combined with radiation therapy, suggesting synergistic activity.<sup>11,12</sup> ATO has also been shown to enhance radiation cell killing in glioblastoma cell cultures and reduce tumor size in xenograft mouse models.<sup>13,14</sup> In vivo mouse studies, conducted by Lew et al., showed selective destruction of mouse tumor vasculature and near-complete blockage of blood flow in the tumor tissue, resulting in central necrosis within 24 h after intratumoral injection of ATO, suggesting antivascular or vascular disrupting effect. This effect was evident in the central hypoxic portion of the intradermal Meth-A tumor causing tumor necrosis.<sup>11</sup> Similarly, a study in rats with intracranial 9L glioma showed shut down of tumor influx and outflow of blood flow to the tumor after 2–4 h of ATO injection. Importantly, the transplanted tumor completely disappeared and the survival time was significantly prolonged after the combined treatment with higher doses of ATO and radiation.<sup>12</sup> Investigators also showed that ATO acutely increased the oxygen consumption rate of tumor cells and showed radiosensitizing effect when combined with radiation in 2 murine liver and lung tumor models.<sup>15</sup> It has also been reported that arsenic could be detected within the brain tissue 2–6 h following administration in humans,<sup>16</sup> and higher levels of arsenic accumulated in brain tumor tissue than in normal brain tissue in rodents.<sup>17</sup>

Glioblastomas invariably contain areas of hypoxia and necrosis that are highly radioresistant, leading to inevitable recurrence, and carry dismal prognosis. The median survival is 15–17 months despite maximal surgical resection followed by adjuvant chemoradiotherapy and adjuvant chemotherapy.<sup>18</sup> The encouraging preclinical results with the vascular-disrupting and radiosensitizing effects of ATO set the stage for this phase I clinical trial. The study was designed to identify the maximum tolerated dose (MTD) of ATO when administered either once-a-week (weekly) or twice-a-week (biweekly) for 6 weeks along with standard radiation in patients with newly diagnosed glioblastoma.

These patients also underwent pharmacodynamic evaluation using perfusion imaging studies.

This multi-institutional phase I study was opened in 2003 within the National Cancer Institute funded New Approaches to Brain Tumor Therapy (NABTT) Consortium which subsequently became the Adult Brain Tumor Consortium. Enthusiasm for this study rapidly waned as the results of the EORTC study comparing radiation alone to radiation with concurrent and adjuvant therapy were published in 2005.<sup>19</sup> Newly diagnosed patients with glioblastoma universally opted for radiation and temozolomide over participation in a phase I study with radiation and arsenic, an agent that had not been tested in this patient population. Rather, research to improve the treatment of glioblastoma focused on intensive and/or longer durations of temozolomide, antiangiogenic agents, targeted therapies, and immunotherapy resulted in premature closure of the study. As a result, the final results of the study were not fully analyzed and the potential effect on survival was not appreciated. With the National Cancer Institute's mandated closure of the Adult Brain Tumor Consortium (ABTC) an effort was made to ensure that all previously conducted studies were fully analyzed and published. That analysis led to the data that is presented in this manuscript. Nevertheless, we report remarkable survival results from this study using ATO in newly diagnosed glioblastoma without temozolomide and the accompanying pharmacodynamic changes on MR imaging.

## Methods

### Patients

Eligible patients were  $\geq 18$  years old, with newly diagnosed glioblastoma (2000 WHO classification when the trial was conducted<sup>20</sup>) with KPS  $\geq 60\%$  and mini-mental score  $\geq 15$ , and no ongoing systemic infections. Patients were required to have plasma transaminases  $< 4$  times above the upper limits of the institutional normal, and potassium  $> 3.0$  and  $< 5.5$  mEq/l, and magnesium  $> 1.2$  and  $< 2.5$  mEq/l. Patients with secondary degree heart block or prolonged QT interval on EKG were excluded as were patients receiving Amphotericin B or any drugs that prolong QT interval or torsade de pointes. Patients could have undergone any extent of surgical resection or biopsy in order to provide a pathologic diagnosis of glioblastoma. The importance of

O<sup>6</sup>-methylguanine-methyl-transferase (MGMT) promotor methylation in tumor DNA or genetic marker studies such as Isocitrate dehydrogenase-1 (IDH-1) was not clinically established when this multi-institutional trial was activated in late 2001 and started patient accrual in March 2003 and completed in 2008. Thus, the study accrued patients with newly diagnosed glioblastoma but no data is available on their MGMT and IDH mutation status. As temozolomide had not been approved when this study was initiated, no patients in this study received temozolomide concurrently with radiation and ATO or in the adjuvant setting. All patients received standard external beam radiotherapy to a total dose of 60 Gy in 30 fractions with the initial 46 Gy targeting the FLAIR imaging abnormality and additional boost treatment of 14 Gy to the contrast enhancing tumor with 1 cm margin. All patients also received ATO (Trisenox®) in escalating doses after assignment to either ATO once-a-week (weekly) each week or twice-a-week (bi-weekly) each week during the 6-week course of radiation therapy. No ATO or other adjuvant chemotherapy was administered following completion of the radiation therapy.

### Study Design and Procedures

This phase I study was an open-label, multi-center safety study conducted by the National Cancer Institute funded New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. The study was registered to ClinicalTrials.gov (NCT00045565). The study was approved by local institutional review boards. All participating patients signed informed consent. At each dose level, 2 treatment schedules opened for accrual simultaneously. When one dose cohort closed, the other cohort would open for enrollment. ATO dose selection was based on the experiences of treatment for promyelocytic leukemia 0.15 mg/kg/day intravenous infusion,<sup>2,3</sup> and for treatment of solid tumors at a higher dose schedule of 0.2 mg/kg/day for 2 weeks on 28 day cycle, and dose-limiting toxicity was reported at a daily dose of 0.35 mg/kg /day.<sup>21,22</sup> Likewise, preclinical results also suggested that the use of higher ATO dose with irradiation might be more efficacious for brain tumors than lower ATO doses.<sup>12</sup> Therefore, a stepwise ATO (Trisenox®) dose escalation was designed in 2 treatment schedules with a starting dose at 0.3 mg/kg once-a-week (weekly) or 0.2 mg/kg twice-a-week (biweekly) given 48 h apart. ATO was infused in 100 ml of 5% dextrose solution over 2 h. ATO dose escalation was in 0.05 mg/kg increments. A cohort of 3 patients were treated at each dose level expanding to a total of 6 patients at the putative maximum tolerated dose (MTD). All adverse events (AEs) were originally recorded per dose cohort using the CTCAE v3 which was the current version when the trial was conducted. However, these data were converted per CTCAE v5 for analysis and reporting possible, probable, or definite toxicities attributable to the treatment. The maximum tolerated dose (MTD) was defined as a dose with less than or equal to a 33% dose limiting toxicities (DLT). The MTDs for the 2 treatment schedules were defined independently. The primary objective of the study was to determine the MTD of ATO when administered on a weekly or biweekly schedule for 6 weeks combined with radiation therapy, and to determine the toxicity profile of ATO administered in conjunction

with radiation therapy in patients with newly diagnosed glioblastoma. Secondary objectives of the study were to determine the overall and progression-free survival of patients after receiving ATO and radiotherapy, and to explore the pharmacodynamic effects of ATO on tumor vasculature by using perfusion MRI.

### Pharmacodynamics

Dynamic susceptibility contrast-perfusion MRIs were obtained at pretreatment baseline, week 1, and week 6 with the combined radiation and ATO treatment. The imaging studies were obtained in patients who were able to tolerate the procedure at the defined time points. Perfusion MRI scan was performed with injection of gadolinium-based contrast agent 0.2 mmol/kg at a flow rate of 4.0 ml/s. The perfusion images were acquired using an Echo Planar Image sequence, with perfusion parameters of mean transit time, relative cerebral blood volume (rCBV), and relative cerebral blood flow (rCBF), time to maximum contrast (TMAX) in the region of interest, and K2. An injection delay of 15 s after the scan was utilized for analysis. Image analysis was performed on studies completed at 3 time points: pretreatment baseline, week 1 and week 6. Regions of interest within the areas of contrast enhancement and/or flair abnormality were compared to the contralateral white matter for a relative estimate of vascular perfusion parameters within the tumor.

### Statistical Analysis

This phase I study followed a 3 + 3 design to define the MTDs of ATO on weekly or biweekly schedules in combination with 6 weeks of standard radiation therapy. The toxicity evaluation period lasted for 10 weeks after the initiation of radiation therapy. The MTD was defined as a dose with a 33% DLT rate and dose escalation took stepwise fashion. All adverse events were reported as probably, possibly, or definitely attributable to the treatment. Patient and disease characteristics, toxicity data, and imaging outcomes were summarized descriptively. Overall survival (OS) and progression-free survival (PFS) times were calculated from the time from surgery or biopsy to death or disease progression, respectively. All patients had died at time of the data analysis. The probability of survival and PFS were estimated using the Kaplan–Meier method.<sup>23</sup> The confidence interval of median survival times was constructed by the Brookmeyer–Crowley method.<sup>24</sup> Survival times were compared between the 2 ATO schedules using the Log-rank test. Perfusion imaging parameters were analyzed between the 2 ATO dose schedules by using the Gehan–Wilcoxon test.<sup>25</sup> All analyses were conducted using SAS software (version 9.2, SAS Institute).

## Results

### Patient Characteristics

Thirty-one patients with newly diagnosed glioblastoma were enrolled in the trial from 4 participating academic institutions between March 2003 and April 2008. Median

age was 54.9 years. Karnofsky performance status was  $\geq 90$  in 77% of the patients. Surgery with either partial or gross total resection was performed in 77%, and biopsy only in 23%. All patients had histologically proven glioblastoma with one being gliosarcoma. Given that this study opened

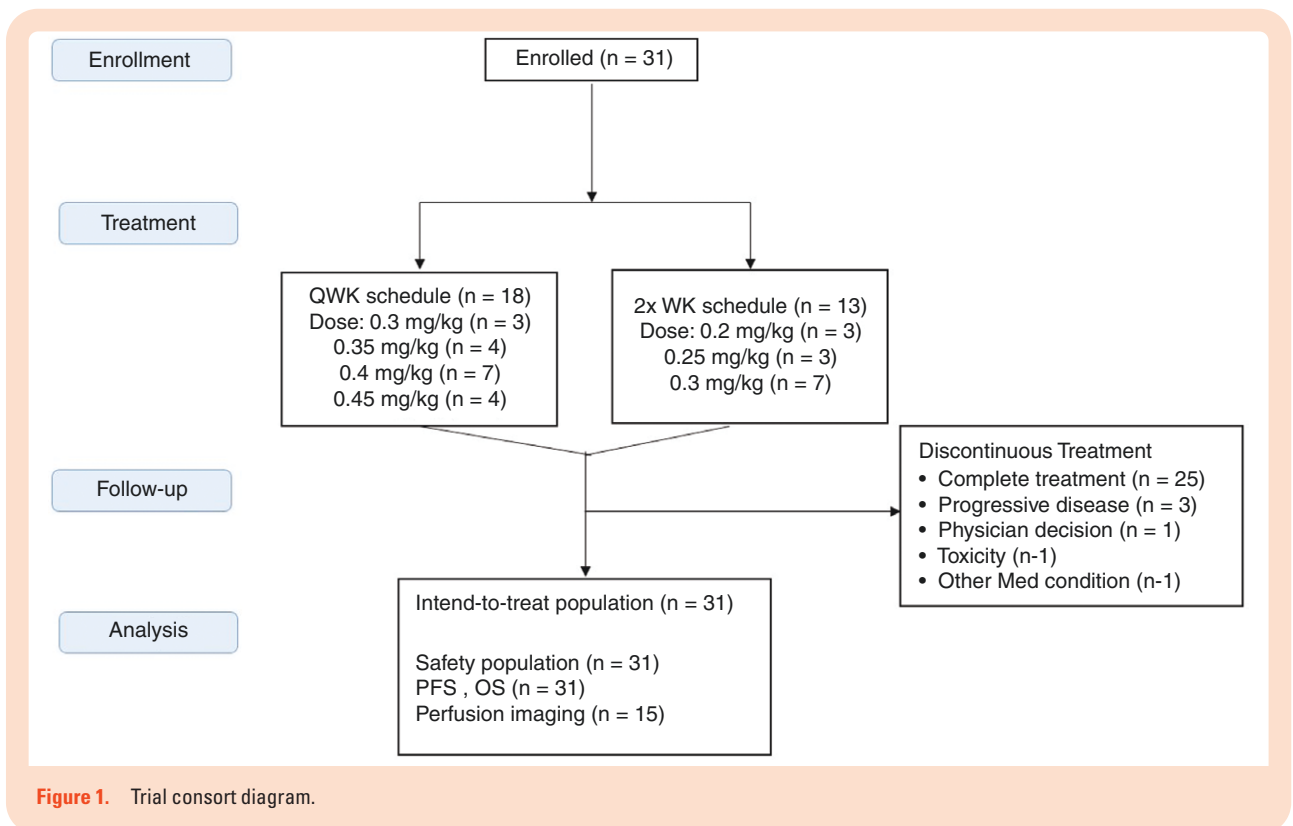
in early 2000's, MGMT and IDH status were not characterized since they were not established for clinical use. The characteristics of patients on the weekly and biweekly ATO schedules are summarized in Table 1. Distribution of baseline patient and disease characteristics was well balanced between the 2 treatment schedules without statistical difference. No patients received concurrent or adjuvant temozolomide or any additional treatment until progression of the tumor. Consort diagram of this trial is shown in Fig. 1.

**Table 1.** Patient Characteristics

	Once a week schedule (n = 18)	Twice a week schedule (n = 13)
Age: Median (Range)	54 (33–75)	52 (24–65)
Race:		
White	17(94%)	9 (69%)
African American	1 (6%)	4 (31%)
Gender: Male/Female	12/6(67%/33%)	9/4 (69%/31%)
KPS:		
90–100	14 (78%)	10(77%)
60–80	4(22%)	3 (23%)
Steroid medication	17 (94%)	10 (77%)
Anticonvulsant medication	17 (94%)	10 (77%)
Histology:		
Glioblastoma Multiforme	18 (100%)	12 (92%)
Gliosarcoma		1 (8%)
Surgery:		
Biopsy	5(28%)	2 (15%)
Craniotomy	13 (72%)	11 (85%)

### Safety and Toxicity With MTD

Patients tolerated the ATO treatment combined with radiotherapy well, with 81% completing the planned 6 weeks of combined treatment. Patients received a median of 6 doses of ATO injections (range: 2–12) during the study. 3 patients discontinued study treatment due to disease progression; one patient withdrew self from the study after one injection, and 2 patients discontinued ATO treatment due to experiencing AEs. Adverse events  $\geq$  grade 3 were observed in 5 patients (3 in weekly schedule and 2 in bi-weekly schedule). At dose level of 0.45 mg/kg weekly ATO injection, there was one patient with a grade 3 DLT of increased aspartate and alanine aminotransferases during the second week, ear and dental pain due to herpes zoster, infection without neutropenia, and hyperkalemia at the end of the planned treatment. At the dose level of 0.3 mg/kg bi-weekly schedule in 7 patients, there was one patient with a grade 3 DLT, having increased alanine aminotransferase and cardiac edema. Thus, the MTD of ATO was determined



to be 0.4 mg/kg for the weekly schedule and 0.3 mg/kg for the biweekly schedule, both in combination with standard radiation therapy. AEs were classified using the CTCAE v3 for data collection at the time of study duration. However, the version 3 data were converted to the version 5 when the data were reanalyzed for reporting. Likewise, details of DLT information and AE grade 3 or higher per CTCAE v5 are listed in Table 2.

### Survival and ATO Schedule

For all patients, the median overall survival was 17.7 months (95%CI: 10.9–22.7) and the median PFS was 5.4 months (95% CI: 3.7–9.5). Each cohort of ATO administration and survival time is summarized in Table 3. Notably, there was a significant difference in survival time between the 2 ATO dose schedules across all dose levels. The median overall survival was 22.8 months (95% CI: 11.7–30.7) in the biweekly schedule versus 12.1 months (95% CI: 4.2–17.7) in the weekly schedule ( $P = .039$ ). There was a similar difference in median PFS; 10.2 months (95% CI: 3.7–18.1)

in the biweekly schedule, vs 3.2 months (95% CI: 3.1–5.4) in the weekly schedule ( $P = .004$ ). The absolute overall and PFS graphs are shown in Figure 2.

### Pharmacodynamic Perfusion Imaging Parameters

Perfusion imaging studies were available in 14 patients for 3 time points at pretreatment baseline, week 1 and week 6. Perfusion imaging parameters, rCBV, rCBF, and K2 significantly decreased at 1 week, and remained decreased at the 6-week scan. Rates of change in the perfusion MRI parameters are shown in the regression plot in Figure 3. Similar to the difference in survival time, there were significant differences in perfusion parameters between the 2 ATO dose schedules. The values of rCBV, rCBF, and K2 were significantly decreased at all the biweekly schedule ATO dose levels as compared to the weekly schedule ( $P = .007$ ). At week 1, rCBF decreased by 7.6 ml blood/100 g tissue/min on average in the biweekly schedule compared to an increase of 5.5 ml blood/100 g tissue/min in the weekly schedule ( $P = .007$ ). The trend remained the same during the 6-week course of treatment. A similar trend was observed in other perfusion parameters between the 2 dose schedules although there was wide variability in the data due to the small total number of patients. Stable tumor response was observed at 6 months in 10 patients (32%) without any additional adjuvant treatment after the combined ATO and radiotherapy; 3 from weekly and 7 from the biweekly ATO schedules.

**Table 2.** Adverse Events Grade  $\geq 3$  With Attributable Causes

Adverse event grade $\geq 3$	Dose and schedule	Grade
Seizure	0.25 mg/kg, biweekly	4, probably
Alanine aminotransferase increased	0.3 mg/kg, biweekly	3, definitely
Cardiac edema	0.3 mg/kg, biweekly	3, possibly
Alanine aminotransferase increased	0.45 mg/kg, weekly	3, definitely
Aspartate aminotransferase increased	0.45 mg/kg, weekly	3, definitely
Ear pain	0.45 mg/kg, weekly	3, unrelated
Shingles	0.45 mg/kg, weekly	3, probably
Toothache	0.45 mg/kg, weekly	3, unrelated
Hypokalemia	0.45 mg/kg, weekly	3, possibly

### Discussion

This phase I study determined the MTD of ATO to be of 0.4 mg/kg when administered weekly and 0.3 mg/kg when given biweekly ATO dose schedules with a standard 6 week course of radiotherapy in patients with newly diagnosed glioblastoma. The combined treatment with ATO and radiation was well tolerated and safe. This study faced genuine challenges in completing accrual and in generating excitement given that shortly after the study opened

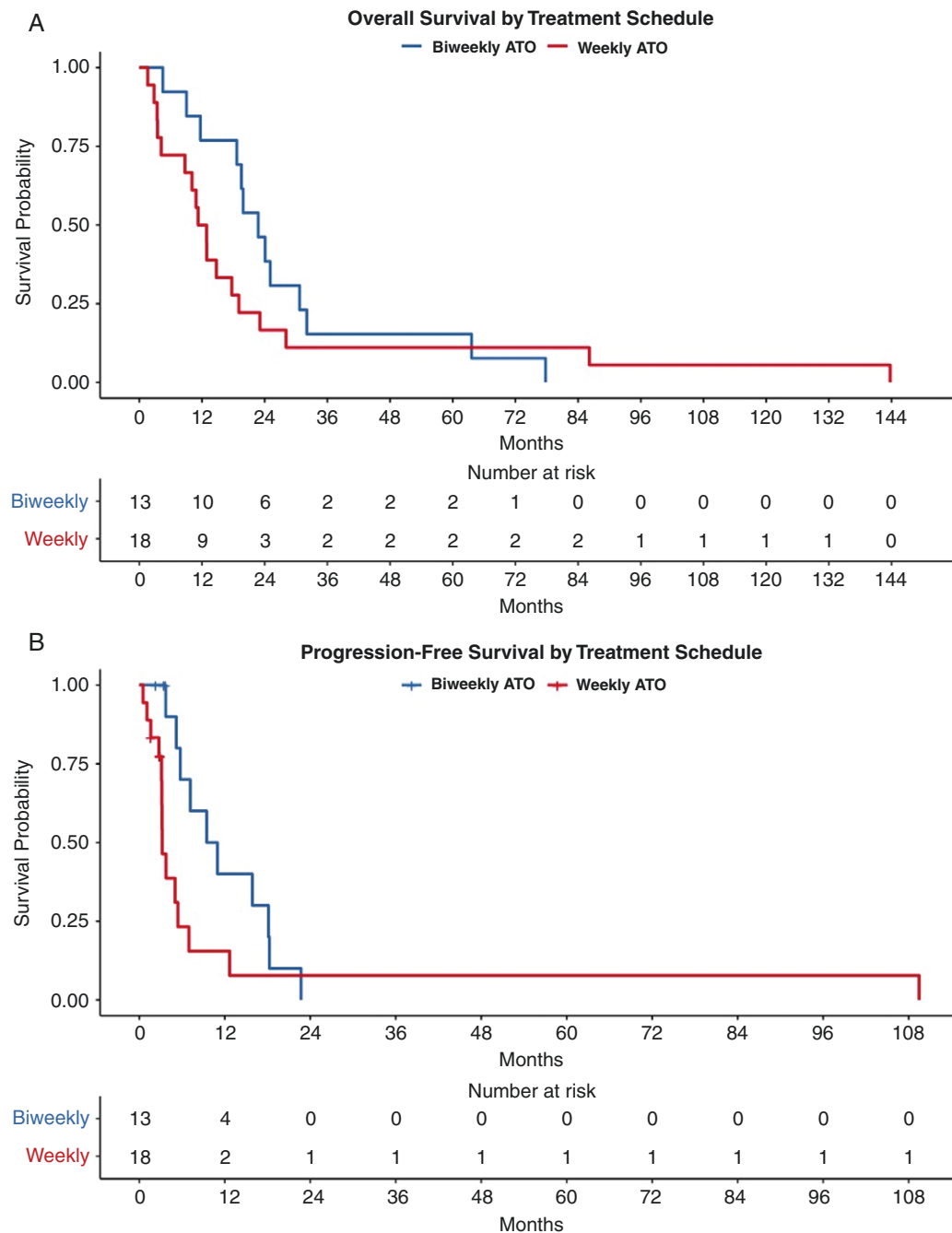
**Table 3.** Tumor Response and Survival Time

ATO dose schedule	Pt No. (n = 31)	Median ATO injections (Range)	Off treatment reason (Pt No.)	Median PFS months (95% CI)	Median OS months (95% CI)
0.2 mg/kg biweekly	3	12 (12–12)		11.0 (5.8–18.1)	25.1 (9–32.1)
0.25 mg/kg biweekly	3	12 (12–12)		20.4 (18.3–22.7)	22.8 (18.7–77.8)
0.3 mg/kg biweekly	7	12 (5–12)	AE (1)	7.1 (3.7–15.9)	19.9 (4.5–63.6)
0.3 mg/kg weekly	3	6 (5–6)		3.2 (2.8–5.0)	19.1 (3.5–86.1)
0.35 mg/kg weekly	4	6 (2–6)	PD (2)	3.8 (1.6–12.7)	6.8 (1.6–17.7)
0.4 mg/kg weekly	7	6 (3–6)	Withdrawal (1)	5.4 (3.1–109.5)	14.8 (10.9–143.7)
0.45 mg/kg weekly	4	4 (2–6)	PD (1), AE (1)	2.1 (0.5–3.2)	6.5 (2.8–12.9)

\* $P = .0009$

\* $P = .0068$

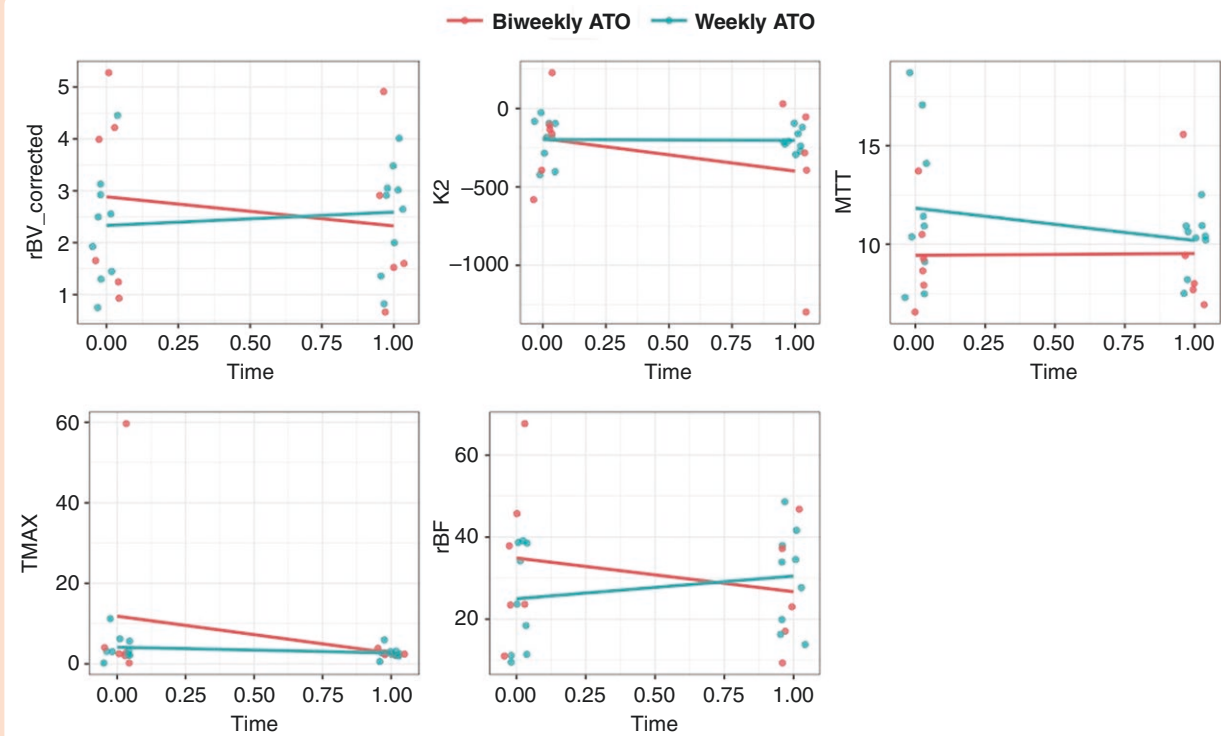
PFS: Progression-free survival, OS: Overall survival, PD: Progressive disease, AE: Adverse effect, \* $P$  values are Log-Rank test between weekly and biweekly schedules.



**Figure 2.** Overall (a) and Progression-free survival (b) curves of weekly and biweekly schedules.

temozolomide was shown to be of benefit in patients with newly diagnosed glioblastoma.<sup>19</sup> As a result, clinicians and patients were hesitant to enroll patients in a study that did not include treatment with this newly approved agent and the study was closed to accrual in 2008 without a formal analysis of the results. With the recent mandated closure of the Adult Brain Tumor Consortium by the National Cancer Institute, an effort was undertaken to formally re-evaluate and where appropriate analyze and publish the results of each ABTC trial. These efforts brought to light the results presented in this manuscript.

There has been a dramatic improvement in our understanding of the role of molecular and genetic markers in patients with glioblastoma with revisions in the classification of glioblastoma and the recognition that IDH mutated and MGMT methylated high grade gliomas are much more likely to benefit from temozolomide.<sup>26,27</sup> But given the paucity of novel therapies and survival has changed little for most patients with glioblastoma, the survival results from this arsenic trial are potentially significant. The median overall survival for all patients in this trial was 17.7 months. These patients were not assessed for MGMT or IDH status



**Figure 3.** Rate of change in perfusion MR imaging parameters at pretreatment baseline, 1 week and 6 week time points, according to weekly and biweekly ATO schedules.

and, as in the EORTC study,<sup>19</sup> one might expect a survival of about 12 months without the use of concurrent and adjuvant temozolomide. The patients who received biweekly ATO in this study had a survival of 22.8 months (vs 12 months in the weekly arm) without concurrent temozolomide or adjuvant chemotherapy. In addition, patients on the biweekly ATO schedule also had significantly decreased rCBF on MRI perfusion studies suggesting a pharmacodynamic effect of ATO on cerebral blood flow in the tumor. Preclinical animal study also showed a similar effect with near-complete blockage of blood flow and necrosis of tumor tissue.<sup>11,12</sup>

These results suggest that ATO may have clinical benefit and that the dose and schedule of ATO may be important. In patients with leukemias, lymphomas, and patients with multiple myeloma ATO is commonly administered daily at doses ranging from 0.15 mg to 0.25 or 0.30 kg/day for different durations.<sup>1-3,21,22</sup> Our study defined the MTD as 0.4 mg/kg weekly and 0.3 mg/kg biweekly administration for 6 weeks. A decade after our study closed, a phase I/II trial with a total of 42 patients (24 in the phase II portion) studied ATO 0.2 mg/kg daily in week 1 then twice a week for 5 weeks, administered with concurrent temozolomide and radiotherapy in patients with newly diagnosed grade III and IV gliomas. They reported median overall survival 17 months and PFS 7 months for patients with glioblastoma.<sup>28,29</sup> The small patient numbers and the mixed grade III and IV glioma populations make historical comparisons difficult, but in retrospect these survival figures are not dissimilar to our findings.

It is not well understood how ATO interacts with radiation. ATO has multiple different mechanisms influencing signal transduction pathways and resulting in a vast range of cellular effects including apoptosis, growth inhibition, promotion or inhibition of differentiation, and angiogenesis inhibition.<sup>7</sup> In leukemia and lymphoma cells, ATO has been shown to promote differentiation of acute promyelocytic leukemia cells at low concentrations, and causes apoptosis at higher concentrations.<sup>30</sup> Additionally in solid tumors, ATO was found to inhibit mitochondrial respiration, decrease the oxygen consumption of tumor cells, and cause tumor radiosensitization.<sup>15</sup> This was more apparent in hypoxic conditions, similar to the findings of a preclinical animal study that demonstrated tumor necrosis in the hypoxic central portion of the tumor, most likely due to selective destruction of tumor vasculature and blockage of blood flow by ATO.<sup>11,12</sup> Our pharmacodynamic finding from perfusion imaging showed decreased rCBF, rCBV, and K<sub>2</sub> within the contrast-enhancing gross tumor, suggesting ATO decreases blood flow and decreases microvascular permeability preferentially within the tumor compared to the surrounding normal brain. This suggests that ATO may exhibit an anti-vascular effect and perhaps differential rheologic effects between tumor and normal brain. Thus, the existing hypoxic areas of glioblastoma would be less perfused and undergo further tumor necrosis, and a relative increase of blood flow in less or nonhypoxic regions of tumor causing radiosensitization. The perfusion MRI parameters can be further explored as a reliable imaging biomarker to predict the effect of combined ATO and radiation for patient selection.

This study demonstrates that ATO can be safely combined with cranial irradiation and establishes the MTD for weekly and biweekly therapy for newly diagnosed glioblastoma. The results suggest that biweekly ATO at the MTD is superior to weekly ATO and this appears to be supported by the pharmacodynamic effect on blood flow with the biweekly therapy. The survival data is provocative but preliminary given the small patient numbers and the lack of MGMT and IDH data. However, we now know that the patients who primarily benefit from the additional of temozolomide are those who are MGMT methylated or IDH mutated.<sup>26,27</sup> Survival may improve by lomustine-temozolomide chemotherapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter.<sup>31</sup> Shorter course of radiation and temozolomide showed longer survival in elderly patients with MGMT methylation, and modest benefit in nonmethylated group.<sup>32</sup> Recent further analysis of patients on EORTC phase III CANTON study revealed that IDH wildtype glioblastoma patients did not benefit from temozolomide over radiotherapy alone regardless of their MGMT methylation status.<sup>33</sup> Although there has been progress in the classification and management of glioblastoma over the past decades, novel agents are required to further improve survival especially in glioblastomas that are MGMT unmethylated and/or IDH wildtype. The encouraging survival information from this study using ATO in newly diagnosed glioblastoma, coupled with the pharmacodynamic imaging data from this study strongly suggests that ATO should be formally evaluated in patients with newly diagnosed glioblastoma where temozolomide is unlikely to improve patient outcomes.

## Keywords

arsenic trioxide | cerebral blood flow | glioblastoma | radiotherapy

## Lay Summary

Glioblastoma (GBM) is a common form of brain cancer. Most patients with GBM eventually die from the disease even after aggressive treatment with surgery, radiation, and chemotherapy. Studies in mice have shown that a compound called arsenic trioxide (ATO) could improve the ability of radiation to kill tumor cells. This study was designed to test the safety of ATO in human patients with GBM and find out the best treatment dose. To do this, the authors recruited 31 patients in a safety trial of the drug. Their results demonstrate that most patients were able to take the drug without major side effects. Patients taking twice a week survived significantly longer than those taking it weekly. Larger clinical trials are needed to confirm these findings.

## Funding

This study was performed by New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium, also known as Adult Brain

Tumor Consortium (ABTC), funded by NCI grant U01 CA62475. The study was registered to ClinicalTrials.gov NCT00045565.

## Acknowledgments

The initial study results were presented at ASCO 2005 and the final results in ASCO 2023. This study concept was based on the experimental results of Dr. Young S. Lew.

## Conflict of interest statement

J.J.O. serves as an editorial consultant for American Cancer Society and receives NCI grant for targeting integrin pathways in medulloblastoma. B.N. receives consulting fees from Chimersx and AnHeart and serves data monitoring board for CNS Pharma. S.A.G. serves advisory board and consulting fee from PlusTherapeutics, and serves scientific advisory board with stock for Myosin. Others have no disclosure.

## Authorship statement

Conception and design: S.R., T.M., S.A.G. Development of methodology: S.R., X.Y., T.M., S.A.G. Acquisition of data: J.J.O., T.M., G.J.L., T.B., B.N., T.W. Analysis and interpretation: S.R., L.B., X.Y., J.J.O., T.W., S.A.G. Writing manuscript review, support: S.R., X.Y., J.J.O., L.B., G.J.L., S.D., T.W., S.A.G.

## Data availability

The original deidentified data generated in the course of the study will be made available upon request. No new data were generated or analyzed in support of this research.

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