

00-C-0070: A Phase I Trial and Pharmacokinetic Study of Arsenic Trioxide in Pediatric Patients with Refractory Leukemia or Lymphoma

Arsenic trioxide (As₂O₃) is an inorganic trivalent arsenical. Preclinical studies demonstrate a dose-dependent induction of apoptosis and partial differentiation in myeloid leukemia cell lines, and induction of apoptosis and cell cycle arrest in lymphoid neoplasms. Since 1971, As₂O₃ has been used in the Northeastern region of China to treat more than one thousand adults with cancer. In clinical trials of adults with relapsed all trans-retinoic acid (ATRA) resistant APL, durable clinical remission with minimal side effects was achieved in 70% of the patients. A phase I trial and pharmacokinetic study of As₂O₃ will be conducted in children. The spectrum of toxicity and the maximum tolerated dose will be defined in pediatric patients with refractory leukemia and lymphoma. All APL patients will be treated with the FDA approved dose of arsenic trioxide (0.15mg/kg/day).

ELIGIBILITY CRITERIA:

Age: Patients with APL must be ≥2 years and ≤12 (twelve) years of age. Patients with non-APL leukemia or lymphoma must be ≥2 years and ≤21 (twenty one) years of age.

Histological diagnosis: Patients must have a leukemia or lymphoma confirmed by morphologic analysis.

- The leukemia/lymphoma must be refractory to standard curative treatment regimens.
- Patients must have had their last dose of radiation therapy at least four weeks prior to study entry, their last dose of chemotherapy at least two weeks prior to study entry (four weeks for nitrosoureas), and their last dose of retinoids 7 days prior to study entry.
- Patients must have recovered from the toxic effects of all prior therapy before entry onto this trial.
- Patients should be off colony stimulating factors such as G-CSF, GM-CSF, and erythropoietin for at least one week prior to study entry.

Measurable/Evaluable disease: Patients must have measurable or evaluable disease.

Performance status: Patients should have an ECOG performance status of 0, 1, or 2.

ECOG Performance Status

Score	Clinical Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden

Hepatic function: Patients must have adequate liver function, defined as bilirubin within normal limits, SGPT < 2x the upper limit of normal.

Renal function: Patients must have an age-adjusted normal serum creatinine (see Table below) OR a creatinine clearance ≥60 mL/min/1.73 m².

Age (Years)	Maximum Serum Creatinine (mg/dl)
< 5	0.8
5 ≤ age <10	1.0
10 ≤ age <15	1.2
≥15	1.5

Serum electrolytes: Potassium, magnesium and calcium must be equal to or greater than the lower limit of the normal range. Oral or intravenous supplementation may be used to normalize the serum electrolytes.

EKG: A rate corrected QT interval (QTc) ≤ 0.48 (See Appendix 8 for the calculation and specific recommendations).

Informed consent: All patients or their legal guardians (if the patients is <18 years old) must sign a document of informed consent indicating their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (This does not include routine laboratory tests or imaging studies required to establish eligibility. The bone marrow sample for biologic studies (Section 3.5) may be obtained prior to the signing of informed consent, but no research studies will be performed on that bone marrow until informed consent is obtained). When appropriate, pediatric patients will be included in all discussions in order to obtain verbal assent.

EXCLUSION CRITERIA

- Patients with meningeal leukemia/lymphomas (CSF WBC $> 5/\text{mm}^3$ and unequivocal confirmation of leukemic blasts in the CSF by morphologic demonstration on a CSF cytocentrifuge specimen). Patients with APL and meningeal disease may be entered following discussion with the PI or Protocol Chairman.
- Patients with persistent grade ≥ 3 (as defined by Common Toxicity Criteria) sensory or motor neuropathy. Patients with APL and persistent grade 3 or 4 neuropathy may be entered following discussion with the PI or Protocol Chairman.
- Patients with history of grand mal seizures (\geq grade 3) other than febrile seizures within the past 2 years. Patients must be off anticonvulsants for a minimum of 6 months. Patients with APL and history of seizures (\geq grade 3) may be entered following discussion with the PI or Protocol Chairman.
- Clinically significant unrelated systemic illness (serious infections or significant cardiac (including dysrhythmias), pulmonary, hepatic, renal or other organ dysfunction) which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate arsenic trioxide or are likely to interfere with the study procedures or results.
- Patients with cardiac disease including dysrhythmias. Patients with APL and history of cardiac disease may be entered following discussion with the PI or Protocol Chairman.
- Patients with normal serum potassium, magnesium, and calcium levels and have a QTc >0.48 after discontinuation of medications that may prolong the QTc interval (See Section 3.7 Concurrent Therapies and Appendix 8).
- Patients with known HIV infection or HIV related lymphoma or lymphoproliferative diseases are excluded from this trial due to unknown interaction of arsenic trioxide with antiretroviral medications and potential biological differences in lymphomas related to immune compromised states.
- Pregnant or breast feeding females are excluded because arsenic trioxide may be harmful to the developing fetus or nursing child.
- Patients currently receiving other investigational agents.
- Patients who previously received arsenic trioxide.

PRETREATMENT EVALUATION:

- History and physical, documentation of signs and symptoms and measurable disease, height, weight, BSA

- Laboratory evaluation (see protocol). Serum Lead level in children < 6 years old
- 24 hr urine for total arsenic
- Bone Marrow Aspiration, and LP within 14 days prior to study entry
- Radiologic evaluation within the 2 weeks prior to start of therapy
- ECG including measurement of QTc within the 2 weeks prior to start of therapy
- Patients should bring to NIH summaries of previous treatment, most recent laboratory work, copies of most recent radiologic studies including 2 scans that document disease progression from last treatment, and original pathology slides and report.

GENERAL TREATMENT PLAN:

- Two cohorts of patients will be studied, APL and non-APL
- All patients >5 years of age with APL will be treated at the FDA approved dose of 0.15 mg/kg/dose
- For the non-APL cohort a fixed dose escalation scheme will be used to determine the MTD. The starting dose for this cohort will be 0.15 mg/kg/day.
- Arsenic trioxide is infused intravenously over 120 minutes daily for 20 doses (five consecutive days per week for 4 weeks) followed by a 2 week break. Induction therapy can be extended for additional 10 days in partial responders. No more than 3 cycles will be given.

PHARMACOKINETICS:

- On the first cycle of therapy blood samples will be drawn immediately prior to and at the end of the infusion, and 0.5, 1, 2, 4, 6, 10, 23 (pre dose 2), 24 (pre dose 2) hours after the end of the infusion. Blood samples should be obtained immediately prior to the dose on day 5 and day 26. Bone marrow and peripheral blood samples will also be collected for biological studies.

ACCRUAL:

- The trial is accruing patients with APL to the 0.15 mg/kg dose level. Accrual to the non-APL stratum is reopened at the 0.20 mg/kg dose level. Patients meeting the eligibility criteria can be referred to the Pediatric Oncology Branch, NCI, for evaluation and treatment on this trial. COG designated Phase I Institutions are also participating in this trial.