

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Trisenox (Arsenic Trioxide)
9/2004

Recommendations:

- Arsenic Trioxide will be added to formulary for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory or have relapsed from retinoid and anthracycline chemotherapy. APL must be characterized by the presence of the t (15; 17) translocation or PML/RAR-alpha gene expression.
- All patients will have an ECG to document the QT interval and current medications will be screened for propensity to cause QT interval prolongation by the pharmacist. <http://www.torsades.org>
- A list of medications with risk of Torsade de Pointes will be provided to the patient.
- ECG will be repeated weekly during therapy.
- If administered in the outpatient infusion center, documentation of weekly ECG will be required by the infusion center.
- If absolute QT is >500 msec, immediately correct risk factors: electrolytes, concomitant drugs, and reassess risk/benefit of continuing versus suspending arsenic trioxide.
- If syncope or rapid or irregular heartbeat occur: Hospitalize and monitor continuously. Hold TRISENOX® until QTc is <460 msec and symptoms resolve.
- 5 HT3 receptor antagonist should be used with caution as some cause QT interval prolongation (Anzemet should not be used).
- Electrolytes will be monitored and kept above the following values:
 - Potassium 4 meq/l
 - Magnesium 1.8 mg/dl
- The patient will be monitored for APL differentiation syndrome:
 - Fever, fluid retention, musculoskeletal pain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis, and dyspnea.
 - Daily patient weight will be recorded and monitored for >2 lbs. gain in 24 hours
 - The patient will be taught the signs and symptoms of APL differentiation syndrome and will be asked to report any symptoms.
 - At the first sign of APL differentiation syndrome, dexamethasone 10 mg BID will be administered and continued for at least 3 days or longer until signs and symptoms have abated.
- A preprinted physician order form will be developed by the Bon Secours Forms Committee for the use of this agent.



Indication:

- Induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory or have relapsed from retinoid and anthracycline chemotherapy.
 - APL must be characterized by the presence of the t (15; 17) translocation or PML/RAR-alpha gene expression.

Mechanism of action: morphological changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells.

Dosage & Administration:

- Induction: 0.15 mg/kg/day until bone marrow remission, maximum of 60 days.
- Consolidation: Begin 3-6 weeks after completion of induction, 0.15 mg/kg daily for 25 does over a period up to 5 week.
- Limited experience with patients < 18 years (5 patients from 5-16 years).
- Admixture in 100-250 ml of 5% Dextrose or 0.9% Sodium Chloride and infuse over 1-2 hours, may be extended up to 4 hours if acute vasomotors reactions occur, by peripheral infusion. A filter needle should be used to withdraw Trisenox form ampule.

Cost Analysis for 70 kg patient			
Approved Dose	Induction	Consolidation	Total Cost
0.15 mg/kg/day	10.5 mg per day for	10.5 mg	
Average Length of therapy	44 days	25 days	
Cost if Dose Rounded Down to 10 mg/day	\$13680.04	\$7772.75	\$21,452.79

Trisenox® is available in 10 mg/10ml vials at a cost of \$3,109.12 for 10 vials.

Warnings & Monitoring:

- APL Differentiation Syndrome occurred in 22.5% (9/40) patients:
 - Characterized by fever, dyspnea, sudden weight gain (> 2 pounds in 24 hours), pulmonary infiltrates, and pleural or pericardial effusions, with or without leukocytosis.
 - Instruct patient to immediately report fever, sudden weight gain (>2 lbs. in 24 hours), musculoskeletal pain, fluid retention, and/or dyspnea.
 - Weigh patient daily to detect weight changes.
 - APL Differentiation Syndrome can be fatal
 - Therapy with high dose steroids (Dexamethasone 10 mg IV BID) should be initiated at the first sign of the disorder. Continue for 3 days or longer, until signs and symptoms resolve
 - Need not interrupt TRISENOX® therapy.
- Weight gain symptomatic of fluid overload, in the absence of a differentiation syndrome, should be treated with potassium-sparing diuretics.
- Hyperleukocytosis:
 - 50% (20/40) of patients developed WBC counts $\geq 10 \times 10^3/\mu\text{L}$

- No association with baseline WBC counts
- Usually self-limiting.
- Chemotherapy not recommended.
- Need not interrupt TRISENOX® therapy.
- 12-lead ECG- baseline; then weekly
 - QT Prolongation:
 - QT/QT_c prolongation is expected
 - Torsade de-pointes and complete heart block has been reported related to concomitant administration of other QT prolonging drugs, a history of torsade de pointes, preexisting QT interval prolongation, CHF, potassium wasting diuretics, hypokalemia, and hypomagnesia.
 - 40% (16/40) of patients had at least 1 ECG with QT_c > 500 msec (460 ECG tracings were reviewed).
 - Usually observed between 1& 5 weeks of infusion and returns to baseline at end of 8 weeks.
 - No correlation with age and sex.
 - More frequently in patients at risk for a cardiac event or if QT increases.
 - Avoid concomitant drugs that prolong QT interval (www.torsades.org) (This List is updated periodically and is not complete-see table.)
 - If absolute QT is >500 msec, immediately correct risk factors: electrolytes, concomitant drugs, and reassess risk/benefit of continuing versus suspending arsenic trioxide.
 - If syncope or rapid or irregular heartbeat occur: Hospitalize and monitor continuously. Hold TRISENOX® until QTc is <460 msec and symptoms resolve.
 - Assess and correct electrolytes.
- Blood Chemistries-weekly
 - Electrolytes- at least twice weekly during induction and at least weekly during consolidation.
 - Maintain serum potassium above 4 mEq/L, and maintain serum magnesium above 1.8 mg/dL.
 - Supplement electrolytes as needed.
 - TRISENOX® can increase blood sugar levels.
 - Caution should be exercised in patients with renal and hepatic impairment.
 - Transient increases in transaminase levels may occur.
 - These events typically do not require dose reduction or interruption of therapy.
 - The safety and effectiveness of TRISENOX® in patients with renal and hepatic impairment has not been studied.
- Rash:
 - Need not interrupt TRISENOX® therapy.
 - Topical steroids are effective.
 - Topical antihistamines for pruritis.

Summary of Monitoring Recommendations

	Before Initiation of Therapy	Twice Weekly	Weekly	Other
ECG	X		Induction and Consolidation	+ prn for clinically unstable patients
Clinical Chemistry Panel (per institution to include electrolytes, BUN, creatinine, glucose, magnesium, and liver function tests)	X		Induction and Consolidation	+ prn
K ⁺ & Mg ²⁺	X	Induction	Consolidation	+ prn
Hematology Profile	X	Induction	Consolidation	+ prn
Coagulation Profile (until normalized)	X	Induction	Consolidation	+ prn
Source: http://www.cticseattle.com/products_mprof.htm				

Drugs with RISK of Torsades de Pointes

Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males, TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males, TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Bepidil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Arelan®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	Restricted availability; Females>Males.
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Motilium®	Anti-nausea / nausea	
Droperidol	Inapsine®	Sedative; Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	Erythrocin®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	E.E.S.®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females>Males
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence	
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	

Revised: 12/17/2002 Source: www.torsades.org

Clinical Trials:

Package insert:

- 40 relapsed or refractory APL patients previously treated with an anthracycline and a retinoid regimen (open-label, single-arm, non-comparative study).
- 0.15 mg/kg/day IV over 1-2 hours until bone marrow was cleared of leukemic cells or up to a maximum of 60 days.
- Complete remission rate was 70% (28/ 40) at a median time of 53 days.
- 3-6 weeks following complete remission, 31 patients received consolidation therapy at the same dose for 25 additional days.
- At follow-up, 18 patients required further treatment with arsenic trioxide as maintenance, and 15 patients had bone marrow transplants.
- At last follow-up (median time 484 days); 27 of 40 (68%) patients were alive and 23 of 40 (58%) remained in complete remission.

All-trans retinoic acid/As₂O₃ combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia.

Proc Natl Acad Sci U S A. 2004 Apr 13;101(15):5328-35. Epub 2004

Shen ZX, Shi ZZ, Fang J, Gu BW, Li JM, Zhu YM, Shi JY, Zheng PZ, Yan H, Liu YF, Chen Y, Shen Y, Wu W, Tang W, Waxman S, De The H, Wang ZY, Chen SJ, Chen Z.

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Both all-trans retinoic acid (ATRA) and arsenic trioxide (As(2)O(3)) have proven to be very effective in obtaining high clinical complete remission (CR) rates in acute promyelocytic leukemia (APL), but they had not been used jointly in an integrated treatment protocol for remission induction or maintenance among newly diagnosed APL patients. In this study, 61 newly diagnosed APL subjects were randomized into three treatment groups, namely by ATRA, As(2)O(3), and the combination of the two drugs. CR was determined by hematological analysis, tumor burden was examined with real-time quantitative RT-PCR of the PML-RAR alpha (promyelocytic leukemia-retinoic acid receptor alpha) fusion transcripts, and side effects were evaluated by means of clinical examinations. Mechanisms possibly involved were also investigated with cellular and molecular biology methods. Although CR rates in three groups were all high (> or =90%), the time to achieve CR differed significantly, with that of the combination group being the shortest one. Earlier recovery of platelet count was also found in this group. The disease burden as reflected by fold change of PML-RAR alpha transcripts at CR decreased more significantly in combined therapy as compared with ATRA or As(2)O(3) mono-therapy (P < 0.01). This difference persisted after consolidation (P < 0.05). Importantly, all 20 cases in the combination group remained in CR whereas 7 of 37 cases treated with mono-therapy relapsed (P < 0.05) after a follow-up of 8-30 months (median: 18 months). Synergism of ATRA and As(2)O(3) on apoptosis and degradation of PML-RAR alpha oncoprotein might provide a plausible explanation for superior efficacy of combination therapy in clinic. In conclusion, the ATRA/As(2)O(3) combination for remission/maintenance therapy of APL brings much better results than either of the two drugs used alone in terms of the quality of CR and the status of the disease-free survival.

Combined treatment with arsenic trioxide and all-trans-retinoic acid in patients with relapsed acute promyelocytic leukemia.

J Clin Oncol. 2003 Jun 15;21(12):2326-34.

Raffoux E, Rousselot P, Poupon J, Daniel MT, Cassinat B, Delarue R, Taksin AL, Rea D, Buzyn A, Tibi A, Lebbe G, Cimerman P, Chomienne C, Femand JP, de The H, Degos L, Hermine O, Dombret H.

Department and Institute of Hematology, Hopital Saint-Louis, Paris, France.

PURPOSE: Arsenic trioxide (ATO) is capable of inducing a high hematologic response rate in patients with relapsed acute promyelocytic leukemia (APL). Preclinical observations have indicated that all-trans-retinoic acid (ATRA) may strongly enhance the response to ATO. **PATIENTS AND METHODS:** Between 1998 and 2001, we conducted a randomized study of ATO alone versus ATO plus ATRA in 20 patients with relapsed APL, all previously treated with ATRA-containing chemotherapy. The primary objective was to demonstrate a significant reduction in the time necessary to obtain a complete remission (CR) in the ATO/ATRA group compared with the ATO group. Secondary objectives were safety and molecular response. **RESULTS:** The CR rate after one ATO with or without ATRA induction cycle was 80%. Clinical and pharmacokinetic observations indicated that the main mechanism of action of ATO in vivo was the induction of APL cell differentiation. Hematologic and molecular response, time necessary to reach CR, and outcome were comparable in both treatment groups. Of 16 CR patients, three patients who reached a molecular remission after one induction cycle had all received chemotherapy for a treatment-induced hyperleukocytosis. Three additional patients who received further additional ATO with or without ATRA cycles converted later to molecular negativity. **CONCLUSION:** ATRA did not seem to significantly improve the response to ATO in patients relapsing from APL. Other potential combinations, including ATO plus chemotherapy, have to be tested.

[An analysis of the therapeutic effects and reactions in treating acute promyelocytic leukemia with intravenous arsenic trioxide or all-trans retinoic acid]

Zhonghua Nei Ke Za Zhi. 1999 Feb;38(2):113-5.

[Article in Chinese]

Zhang X, Yang L, Qiao Z.

The Institute of Hematology, Shanxi Medical University, Taiyuan, 030001.

OBJECTIVE: To compare the therapeutic effects and reactions of intra venous arsenic trioxide and all-trans retinoic acid in treating patients with acute promyelocytic leukemia (APL). **METHODS:** 75 cases of APL were randomized either to arsenic trioxide (37) or to all-trans retinoic acid (38). The rates of complete remission (CR), disease free survival (DFS) and side effects were observed. **RESULTS:** In the two groups of patients with APL, the rate of CR was 86.4% and 84.2%. There was also no significant difference in the rate of DSF phase of CR ($P > 0.05$). The side effects of these two medications in therapeutic dose were mild and there was no cross resistance between them. **CONCLUSION:** Arsenic trioxide can lead to apoptosis of leukemic cells and might be a new promising drug to induce differentiation.

Cardiac monitoring of patients receiving arsenic trioxide therapy.

Unnikrishnan D, Dutcher JP, Garl S, Varshneya N, Lucariello R, Wiernik PH.

Our Lady of Mercy Cancer Center, 600 East 233rd Street, Bronx, NY, USA.

Br J Haematol. 2004 Mar;124(5):610-7.

Arsenic trioxide (ATO) is approved for the treatment of acute promyelocytic leukaemia and is under investigation for other malignancies. We report the cardiac findings in 18 patients with haematologic

malignancies treated with ATO and assess the role of cardiac factors in fluid retention syndrome observed during ATO therapy. Based on initial observations in 10 patients treated with ATO, cardiac functions in the subsequent eight patients were evaluated prospectively. Evaluation included pre- and during-treatment electrocardiograms, Holter monitoring, echocardiograms, multigated acquisition scan and cardiac stress tests if indicated. All eight patients developed fluid retention during ATO, evidenced by pulmonary congestion, oedema and pleural/pericardial effusions. No cardiac factors were identified that contributed to fluid retention. Six patients had prolonged corrected QT (QTc) compared with baseline, three developed ventricular tachycardia. Sinus tachycardia, ventricular premature contractions, and non-sustained ventricular/supraventricular tachycardia were seen during ATO treatment. Fluid retention and cardiac events did not correlate with the dose or total amount of ATO or prior anthracycline therapy. In summary, fluid overload during ATO therapy does not appear to be cardiac in origin but appears to be drug-related, and may reflect cytokine-induced capillary leak. QTc prolongation, transient arrhythmias and clinically significant arrhythmias were seen with therapeutic doses of ATO.

Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide.

Blood. 2001 Jul 15;98(2):266-71.

Westervelt P, Brown RA, Adkins DR, Khoury H, Curtin P, Hurd D, Luger SM, Ma MK, Ley TJ, DiPersio JF.

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Arsenic trioxide has been shown to be effective in treating acute promyelocytic leukemia (APL), with minimal overall toxicity reported to date. A phase I/II study was initiated in June 1998 using arsenic trioxide for relapsed APL to determine the maximum tolerated or minimal effective dose and to determine the efficacy of treatment at that dose. Ten patients received 1 to 4 monthly cycles of treatment with 0.1 mg/kg per day intravenous arsenic trioxide. Six of 7 patients evaluable for response achieved cytogenetic or molecular complete remission. However, 3 patients died suddenly during the first cycle of treatment. Autopsies obtained on 2 of these failed to identify a cause of sudden death, despite evidence of pulmonary hemorrhage in one. A third patient, for whom an autopsy was not performed, became asystolic and died while on continuous cardiac telemetry. These observations suggest that arsenic trioxide may be significantly or even fatally toxic at doses currently used and that caution is warranted in its use.