BC Cancer Protocol Summary for Induction and Consolidation Therapy of Relapsed Acute Promyelocytic Leukemia using Arsenic Trioxide and Tretinoin (All-Trans Retinoic Acid)

Protocol Code	*LKATOR*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Sujaatha Narayanan*

ELIGIBILITY:
Acute promyelocytic leukemia (APL) with t(15;17) translocation and PML/RAR-alpha gene expression:
- Relapsed after first-line therapy, including arsenic trioxide based regimens, or
- Refractory to non-arsenic trioxide based regimens

EXCLUSIONS:
- Total bilirubin greater than 51 micromol/L
- Baseline QTc greater than 500 msec

TESTS:
- *Baseline:*
  - CBC & Diff, platelets, sodium, potassium, calcium, magnesium, phosphate, urea, creatinine, alkaline phosphatase, ALT, total and direct bilirubin, LDH, albumin, uric acid, INR, PTT, fibrinogen, HSV, VZV, HBsAg, HBsAb, HBcAb, ECG, serum HCG (in women of child bearing potential)
- *Induction* (inpatient):
  - Daily: CBC & Diff, platelets, sodium, potassium, magnesium, urea, creatinine
  - Twice weekly: Alkaline phosphatase, ALT, AST, GGT, total and direct bilirubin, albumin, LDH, calcium, phosphate, random glucose
  - Weekly: Fibrinogen, INR, PTT
- *Consolidation* (outpatient):
  - Three times a week while receiving arsenic, and weekly while off arsenic: CBC & Diff, platelets, sodium, potassium, magnesium, urea, creatinine, alkaline phosphatase, ALT, GGT, total and direct bilirubin, LDH, calcium, phosphate, albumin
  - Weekly during arsenic weeks and as clinically indicated: ECG
  - Weekly during consolidation and as clinically indicated: INR, PTT, random glucose
  - Day 1 of each arsenic consolidation cycle for women of child bearing potential: Serum HCG

PREMEDICATIONS:

- Optional during consolidation:
  - prochlorperazine 10 mg PO x 1 dose 30 to 60 minutes prior to arsenic trioxide
  or
  - metoclopramide 20 mg PO x 1 dose 30 to 60 minutes prior to arsenic trioxide

SUPPORTIVE MEDICATIONS:

- If HSV and/or VZV seropositive: valACYClovir 500 mg PO BID, until at least 1 month after completion of all cycles of arsenic trioxide OR at the discretion of the physician

TREATMENT:

Drug	**Induction Dose**	**BC Cancer Administration Guideline**
tretinoin	22.5 mg/m^2* BID on Days 1 to 35** (Total daily dose = 45 mg/m^2/day)	PO
arsenic trioxide	0.15 mg/kg once daily on Days 1 to 35	IV in 100 mL NS over 2 h

* Round to nearest 10 mg
** Continue until hematologic complete remission or for a maximum of 60 days

Drug	**Consolidation Dose***	**BC Cancer Administration Guideline**
arsenic trioxide	0.15 mg/kg once daily for 5 consecutive days per week for 5 weeks	IV in 100 mL NS over 2 h

* Usually starts one week after end of induction

Note: Dosing of arsenic trioxide based on total body weight in obese patients may result in higher than expected plasma and tissue concentrations in obese patients. Monitor all obese patients closely for signs of acute arsenic toxicity.

DOSE MODIFICATIONS:

1. **Non-hematological**

Dose levels for toxicities (except hepatotoxicity and QTc prolongation)

Dose Level	arsenic trioxide (mg/kg) once daily	tretinoin (mg/m^2) BID*
Start level 0	0.15	22.5
-1	0.11	18.75
-2	0.10	12.5
-3	0.075	10

* Round to nearest 10 mg

2. **Hematological:** NO dose reduction during induction

ANC (x 10^9/L)		Platelets (x 10^9/L)	Duration	Dose
Less than 1.0	or	Less than 50	More than 5 weeks	Reduce by one dose level
Less than 1.0	or	Less than 50	More than 50 days or occurs on 2 consecutive courses	Send bone marrow aspirate for RT-PCR analysis of PML/RARA. If persisting molecular complete remission, resume at one dose level lower than the previous dose.

3. **Liver dysfunction:**

Hepatotoxicity	Dose
Grade 3-4	▪ Hold until total and direct bilirubin and/or AST and/or alkaline phosphatase below 4 x ULN ▪ Resume at 50% of previous dose during the first week. ▪ Increase to full dose if no further worsening. ▪ If hepatotoxicity reappears, discontinue both drugs.

4. **QT prolongation**

QTc interval	Dose of arsenic trioxide

Greater than 500 msec*	• Hold dose until QTc less than 500 msec*
	• Resume as below if no prolongation after each escalation:
	  • Week 1: 0.075 mg/kg
	  • Week 2: 0.11 mg/kg
	  • Week 3 and thereafter: 0.15 mg/kg

*Calculate corrected QT interval (in msec) using Framingham formula [QTc = QT + 0.154 (1 – 60/HR)]

5. **Other non-hematological toxicities:**

Toxicity	Dose (arsenic trioxide and tretinoin)
Grade 2	Reduce by 1 dose level
Grade 3-4	Hold until less than grade 2, then resume at two dose level reduction

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BMT/Leukemia Febrile Neutropenia Guidelines.
2. **Renal dysfunction:** patients with creatinine clearance less than 30 mL/min may require dose reduction of arsenic trioxide and tretinoin.

3. **Acute arsenic toxicity** presents with convulsions, muscle weakness, confusion, and ECG abnormalities.
4. **APL differentiation syndrome (DS)** is defined as unexplained fever, dyspnea, pleural and/or pericardial effusion, pulmonary infiltrates, renal failure, hypotension, and unexplained weight gain greater than 5 kg. Severe DS is defined as 4 or more of these signs or symptoms and moderate DS is defined as 2 or more signs and symptoms. Dexamethasone 10 mg IV BID should be initiated.
5. **Leucocytosis** may develop after treatment initiation. Patients can be treated with hydroxyUREA 500 mg QID for WBC 10-50 x 10^9/L or 1000 mg QID for WBC greater than 50 x 10^9/L. Discontinue hydroxyUREA when WBC less than 10 x 10^9/L.
6. **QTc prolongation:** Arsenic trioxide is associated with QTc prolongation. Monitor ECG at baseline, weekly during arsenic trioxide therapy, and as clinically indicated. Treatment interruption and subsequent dose reduction is required for development of QTc prolongation (QTc > 500 msec). Correct electrolyte abnormalities prior to treatment, and maintain serum potassium above 4 mmol/L and serum magnesium within normal limits during arsenic trioxide therapy. Use caution in combination with other medications also associated with QTc prolongation.
7. **Transient, mild headache** may occur several hours after tretinoin ingestion.
8. **Hypervitaminosis A syndrome** have been observed with tretinoin, including xeroderma, lip and mouth dryness, cheilitis, rash, edema, nausea, vomiting and bone pain.
9. **Benign or idiopathic intracranial hypertension** (pseudotumour cerebri) may occur with an onset of about 3-17 days of tretinoin therapy.
10. **Venous and arterial thrombosis** is a risk during the first month of tretinoin treatment.
11. **Hepatitis B Reactivation**: All patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.

Call Dr. Sujaatha Narayanan or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1 Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 1998;339(19):1341-48.

2 Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19(18):2852-60.