LKATOPBC Cancer Protocol Summary for First-Line Induction and Consolidation Therapy of Acute Promyelocytic Leukemia using Arsenic Trioxide, Tretinoin (All-Trans Retinoic Acid) and DAUNOrubicin

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

ELIGIBILITY:

- Newly diagnosed acute promyelocytic leukemia (APL) with high risk (WBC more than 10 x 10^9/L)

EXCLUSIONS:

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

TESTS:

- *Baseline*:
  - CBC & Diff, 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, HBcoreAb, ECG, serum HCG (in women of child bearing potential), Radionuclide ventriculography/Echocardiogram to assess LVEF
  - Send peripheral blood to Cancer Genetics Laboratory for baseline MRD assessment for PML/RARA prior to commencement of arsenic and DAUNOrubicin.
- *Induction:*
  - Daily: CBC & Diff, 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
  - If clinically indicated: HBV viral load
- *Consolidation*:
  - Three times a week while receiving arsenic, and weekly while off arsenic: CBC & Diff, 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 (Day 1 of Weeks 1, 9, 17, and 25): Serum HCG
  - If clinically indicated: HBV viral load

DISEASE MONITORING:

- Post Induction: Bone marrow to confirm morphological remission (karyotype, FISH, MRD are not indicated)
- Post consolidation: Peripheral blood MRD assessment for PML/RARA on completion of all planned consolidation cycles to confirm a molecular remission. Following confirmation of molecular remission please perform peripheral blood MRD assessments 3 monthly for 3 years
- CBC & Diff, platelets monthly for 5 years is recommended

PREMEDICATIONS:

- Induction:
  - ondansetron 8 mg PO BID while on DAUNOrubicin treatment
- Optional during consolidation:
  - metoclopramide 20 mg PO x 1 dose 30 to 60 minutes prior to arsenic trioxide

  or
  - prochlorperazine 10 mg PO x 1 dose 30 to 60 minutes prior to arsenic trioxide

SUPPORTIVE MEDICATIONS:

- predniSONE 0.5 mg/kg (round to nearest 5 mg) once daily on Days 1 to 31 or until end of induction therapy, then taper over 7 to 10 days.
- If HSV and/or VZV seropositive: valACYClovir 500 mg PO BID
  Continue valACYClovir until at least 1 month after completion of all cycles of arsenic OR at the discretion of the physician
- Moderate to high risk of hepatitis B reactivation, depending on serology. If HBsAg, or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines.

TREATMENT:

Drug	Induction Dose	BC Cancer Administration Guideline
tretinoin	22.5 mg/m^2* BID on Days 1 to 60** (Total daily dose = 45 mg/m^2/day)	PO
DAUNOrubicin	60 mg/m^2 once daily on Days 1 to 3	IV in 100 mL NS or D5W over 30 min
arsenic trioxide	0.15 mg/kg once daily on Days 4 to 31**	IV in 100 mL NS over 2 h

* Round to nearest 10 mg

** Continue onto Day 63 if not in morphological complete remission at Day 31

Drug	Consolidation Dose*	BC Cancer Administration Guideline
tretinoin	22.5 mg/m^2** BID on: ▪ Weeks 1 to 2 ▪ Weeks 5 to 6 ▪ Weeks 9 to 10 ▪ Weeks 13 to 14 ▪ Weeks 17 to 18 ▪ Weeks 21 to 22 ▪ Weeks 25 to 26 (Total daily dose = 45 mg/m^2/day)	PO
arsenic trioxide	0.15 mg/kg once daily for 5 consecutive days per week on: ▪ Weeks 1 to 4 ▪ Weeks 17 to 20 ▪ Weeks 9 to 12 ▪ Weeks 25 to 28	IV in 100 mL NS over 2 h

* Usually starts one week after end of induction

** Round to nearest 10 mg

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.

Consolidation dosing schema:

	Wk 1	***Wk 2***	***Wk 3***	***Wk 4***	***Wk 5***	***Wk 6***	***Wk 7***	***Wk 8***
tretinoin	Days 1-14		rest	rest	✓	✓	rest	rest
arsenic trioxide	Days 1-5	Days 1-5	Days 1-5	Days 1-5	rest	rest	rest	rest
	Wk 9	***Wk 10***	***Wk 11***	***Wk 12***	***Wk 13***	***Wk 14***	***Wk 15***	***Wk 16***
tretinoin	Days 1-14		rest	rest	✓	✓	rest	rest
arsenic trioxide	Days 1-5	Days 1-5	Days 1-5	Days 1-5	rest	rest	rest	rest
	Wk 17	***Wk 18***	***Wk 19***	***Wk 20***	***Wk 21***	***Wk 22***	***Wk 23***	***Wk 24***
tretinoin	Days 1-14		rest	rest	✓	✓	rest	rest
arsenic trioxide	Days 1-5	Days 1-5	Days 1-5	Days 1-5	rest	rest	rest	rest
	Wk 25	***Wk 26***	***Wk 27***	***Wk 28***				
tretinoin	Days 1-14		rest	rest				
arsenic trioxide	Days 1-5	Days 1-5	Days 1-5	Days 1-5				

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 (both drugs)
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 (arsenic trioxide and tretinoin)
Grade 3-4	▪ Hold until total and direct bilirubin and/or ALT 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.

Total bilirubin (micromol/L)	Dose (DAUNOrubicin)
Less than 26	100%
26 to 51	75%
52 to 85	50%
Greater than 85	hold

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. Cardiotoxicity: DAUNOrubicin only

Ejection Fraction	DAUNOrubicin Dose
50% or greater	60 mg/m^2
40 to 49%	45 mg/m^2
35 to 39%	30 mg/m^2
less than 35%	hold dose

6. **Renal toxicity: DAUNOrubicin only**
   - Reduce dose by 50% if creatinine greater than 265 micromol/L

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

Toxicity	Dose (arsenic trioxide and tretinoin)
Grade 2	Reduce by one 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. **Cardiac Toxicity**: DAUNOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if lifelong dose of 450 mg/m^2 to be exceeded. (See BC Cancer Drug Manual).
3. **Extravasation**: DAUNOrubicin causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Renal dysfunction:** patients with creatinine clearance less than 30 mL/min may require dose reduction of arsenic trioxide and tretinoin.
5. **Acute arsenic toxicity** presents with convulsions, muscle weakness, confusion, and ECG abnormalities.
6. **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.
7. **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.
8. **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.
9. **Transient, mild headache** may occur several hours after tretinoin ingestion.

10. **Hypervitaminosis A syndrome** have been observed with tretinoin, including xeroderma, lip and mouth dryness, cheilitis, rash, edema, nausea, vomiting and bone pain.
11. **Benign or idiopathic intracranial hypertension** (pseudotumour cerebri) may occur with an onset of about 3-17 days of tretinoin therapy.
12. **Venous and arterial thrombosis** is a risk during the first month of tretinoin treatment.
13. **Hepatitis B Reactivation**: See SCHBV protocol for more details.

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. Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood 2010;116(19):3751-7.
2. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 1998;339(19):1341-48.
3. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood 2006;107(9):3469-73.