BC 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:

- Bilirubin greater than 51 micromol/L
- Baseline QTc greater than 500 msec

TESTS:

- Bloodwork:
  - *Baseline*:
    - CBC and differential, platelets, sodium potassium, calcium, magnesium, phosphate, urea, serum creatinine, alkaline phosphate, ALT, bilirubin, LDH, albumin, uric acid, INR, PTT, fibrinogen, HSV, HBsAg, HBsAB, HBcAb
    - Send peripheral blood to Cancer Genetics Laboratory for baseline MRD assessment for PML/RARA prior to commencement of arsenic and DAUNOrubicin.
  - Inpatient: serum magnesium and potassium daily
  - Send peripheral blood to Cancer
  - *Every visit*: CBC and differential, platelets, sodium potassium, magnesium, urea, serum creatinine
  - *Three times a week*: alkaline phosphate, ALT, bilirubin, LDH, calcium, phosphate
  - *Weekly and as clinically indicated:* uric acid, INR, PTT, fibrinogen
- ECG: baseline, then weekly and as clinically indicated
- Radionuclide ventriculography/Echocardiogram: baseline to assess LVEF
- serum-HCG: baseline in all women of child bearing potential

DISEASE MONITORING:

- Post Induction: bone marrow to confirm morphological remission (not cytogenetic). FISH studies can be performed but will not alter management.
- Post consolidation: bone marrow with 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.

PREMEDICATIONS:

- ondansetron 8 mg PO BID while on DAUNOrubicin treatment
- metoclopramide 10 to 20 mg IV/PO Q6H PRN
- prochlorperazine 10 mg PO Q6H PRN

SUPPORT MEDICATIONS:

- predniSONE 0.5 mg/kg (round to nearest 5 mg) once daily on Days 1 to 60 or until end of induction therapy, then taper over 7 to 10 days.
- If HSV and/or HZV 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
- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.
- If admission serum potassium below 4 mmol/L, potassium chloride 20 mmol PO BID
- If admission serum magnesium below 0.7 mmol/L, magnesium complex 100 mg PO BID

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)	tretinoin (mg/m^2)
Start level 0	0.15	45
-1	0.11	37.5
-2	0.10	25
-3	0.075	20

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

ANC (x 10^9/L)		Platelets (x 10^9/L)	Duration	Dose (arsenic trioxide and tretinoin)
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 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.

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 the corrected QT interval using the 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. Hepatotoxicity: DAUNOrubicin only

Bilirubin (micromol/L)	*Dose Modification*
Less than 26	100%
26 to 51	75%
52 to 85	50%
Greater than 85	hold

7. Renal toxicity: DAUNOrubicin only

Reduce dose by 50% if creatinine greater than 265 micromol/L

8. 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. (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. **Transient, mild headache** may occur several hours after tretinoin ingestion.
9. **Hypervitaminosis A syndrome** have been observed with tretinoin, including xeroderma, lip and mouth dryness, cheilitis, rash, edema, nausea, vomiting and bone pain.
10. **Benign or idiopathic intracranial hypertension** (pseudotumour cerebri) may occur with an onset of about 3-17 days of tretinoin therapy.
11. **Venous and arterial thrombosis** is a risk during the first month of tretinoin treatment.

12. **Hepatitis B Reactivation**: All patients should be tested for HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine during the chemotherapy and for six months afterwards. The patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two 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. 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.