

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

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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:

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

TESTS:

- Bloodwork:
 - Baseline: HSV, HZV, HBsAg, HBsAB, HBcAb
 - If inpatient:
 - Daily serum magnesium and potassium
 - If outpatient:
 - Day 1, then three time weekly
 - CBC and differential, platelets, sodium,, potassium, urea, serum creatinine, GGT, ALP, ALT, AST, bilirubin (total and direct), LDH, albumin, calcium, magnesium, phosphate
 - Day 1, then weekly:
 - INR, PTT, fibrinogen
- ECG
 - Baseline, then weekly and as clinically indicated

PREMEDICATIONS:

- prochlorperazine 10 mg PO Q6H PRN
- metoclopramide 10 to 20 mg PO/IV Q6H PRN

SUPPORT MEDICATIONS:

- predniSONE 0.5 mg/kg (round to nearest 5 mg) PO once daily on Days 1 to 60 or until end of induction therapy
- If HSV and/or HZV 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
- 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	<u>Induction</u> 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
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

*** Round to nearest 1 mg

Drug	<u>Consolidation</u> 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

** Round to nearest 1 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.

DOSE MODIFICATIONS:

1. Non-hematological

Dose levels for toxicities (except hepatotoxicity and QTc prolongation)

Dose Level	arsenic trioxide (mg/kg)
Start level 0	0.15
-1	0.11
-2	0.10
-3	0.075

2. Hematological:

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	<ul style="list-style-type: none">Hold until bilirubin and/or AST and/or alkaline phosphatase below 4 x ULNResume 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	<ul style="list-style-type: none"> • Hold dose until QTc less than 500 msec* • Resume as below if no prolongation after each escalation: <ul style="list-style-type: none"> • 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. Other non-hematological toxicities:

Toxicity	Dose
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.
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 10⁹/L or 1000 mg QID for WBC greater than 50 x 10⁹/L. Discontinue hydroxyUREA when WBC less than 10 x 10⁹/L.
6. **Hepatitis B Reactivation:** All patients should be tested for HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally for the entire duration of 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 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.