

## Regimen Reference Order

### LEUK – VESANOID® (ATRA) + arsenic trioxide consolidation (APL)

ARIA: LEUK - [ATRA + arsenic trioxide (APL)]

Planned Course: 7 Cycles (1 cycle = 28 days)

Indication for Use: Acute Prolymyelocytic Leukemia; Consolidation; Low to Intermediate Risk

CVAD: At Provider's Discretion

#### Proceed with treatment if:

##### **Day 1 of Cycles 1, 3, 5 and 7 (ATRA + arsenic trioxide)**

- ANC equal to or greater than  $1.5 \times 10^9/L$  AND Platelets equal to or greater than  $100 \times 10^9/L$
- Potassium level greater than 4 micromol/L (preferably in the high normal range)
- Magnesium level greater than 0.74 micromol/L (preferably in the high normal range)
- QTcF is less than 500 msec
- Creatinine Clearance greater than 30 mL/minute
- Total bilirubin less than 51 micromol/L

##### **Day 1 of Cycles 2, 4 and 6 (ATRA only)**

- Proceed regardless of CBC
- ❖ Contact Leukemia/BMT (L/BMT) Physician if parameters not met

## SEQUENCE OF MEDICATION ADMINISTRATION

### Pre-treatment Requirements

| Drug           | Dose | CCMB Administration Guideline |
|----------------|------|-------------------------------|
| Not Applicable |      |                               |

### Treatment Regimen\*

#### LEUK – VESANOID® (ATRA) + arsenic trioxide consolidation (APL)

| Establish primary solution 500 mL of: normal saline               |   |  |
|---|---|--|
| Drug  | Dose  | CCMB Administration Guideline  |
| <b>Cycles 1, 3, 5 and 7 – VESANOID® (ATRA) + arsenic trioxide</b> |   |  |
| VESANOID® (ATRA)  | 45 mg/m <sup>2</sup> /day<br>(to nearest 10 mg) | Orally divided twice daily on <b>Days 1 to 14</b> , followed by 14 days off<br>Take with food. Swallow whole<br><b>(Self-administered at home)</b> |
| <b>Days 1 to 5</b>  |   |  |
| arsenic trioxide  | 0.15 mg/kg                                      | IV in normal saline 100 mL over 2 hours  |
| <b>Days 8 to 12</b>   |   |  |
| arsenic trioxide  | 0.15 mg/kg                                      | IV in normal saline 100 mL over 2 hours  |

| <b>Days 15 to 19</b>  |   |  |
|---|---|--|
| arsenic trioxide  | 0.15 mg/kg                                      | IV in normal saline 100 mL over 2 hours  |
| <b>Days 22 to 26</b>  |   |  |
| arsenic trioxide  | 0.15 mg/kg                                      | IV in normal saline 100 mL over 2 hours  |
| <b>Cycles 2, 4 and 6 – VESANOID® (ATRA)</b>   |   |  |
| VESANOID® (ATRA)  | 45 mg/m <sup>2</sup> /day<br>(to nearest 10 mg) | Orally divided twice daily on <b>Days 1 to 14</b> , followed by 14 days off<br>Take with food. Swallow whole<br><b>(Self-administered at home)</b> |
| All doses will be automatically rounded that fall within CCMB Approved Dose Bands. See Dose Banding document for more information                             |   |  |
| <b>*See Appendix A – Consolidation dosing schema (low risk or intermediate risk group)</b>  |   |  |
| all-trans retinoic acid (VESANOID®) available dosage strength: 10 mg capsule<br>Classification: Non-Cytotoxic, Hazardous                                      |   |  |
| ***** <b>Note: ATRA = all-trans retinoic acid = tretinoin = VESANOID®</b> *****<br><i>Not to be confused with isotretinoin (ACUTANE®, EPURIS® or CLARUS®)</i> |   |  |

In the event of an infusion-related hypersensitivity reaction, refer to the 'Hypersensitivity Reaction Standing Order'

## REQUIRED MONITORING

### Baseline

- CBC, serum creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, ALK, AST, ALT, total bilirubin, LDH, albumin, uric acid, cholesterol, triglycerides, INR, PTT and fibrinogen as per Physician Orders
- EKG

### Cycles 1, 3, 5 and 7 (VESANOID® (ATRA) + arsenic trioxide)

Twice per week and as clinically indicated

- CBC, serum creatinine, urea and electrolytes including sodium, potassium and magnesium as per Physician Orders

At least once weekly and as clinically indicated

- uric acid, ALK, AST, ALT, total bilirubin, LDH and electrolytes including calcium and phosphate as per Physician Orders
- EKG. Contact Leukemia/BMT (L/BMT) Physician for direction if QTcF is equal to or greater than 500 msec

### arsenic trioxide monitoring

- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O<sub>2</sub> saturation) immediately prior to and immediately after each dose and as clinically indicated
- No observation period is required. Patient can be discharged from treatment room if stable whether they had a reaction or not

### Cycles 2, 4 and 6 (VESANOID® (ATRA))

Prior to each cycle

- CBC and full biochemistry

### Recommended Support Medications

| Drug          | Dose | CCMB Administration Guideline |
|---------------|------|-------------------------------|
| None required |      |                               |

### DISCHARGE INSTRUCTIONS

- Patients should be instructed to monitor for and report any treatment related side effects. This may include edema, abdominal pain, diarrhea, nausea, vomiting, dizziness, headache or cough
- Instruct patient to report shortness of breath or signs/symptoms of arrhythmias (dizziness, palpitations or fainting)
- VESANOID® (ATRA) has potential for significant drug-drug interactions. Patients should notify clinic prior to starting any new medication
- Avoid grapefruit and grapefruit juice, Seville oranges (i.e. orange marmalade) and starfruit
- Reinforce safe handling precautions of medications, blood and body fluids for 48 hours after completion of arsenic trioxide

### ADDITIONAL INFORMATION

- No central line is required for the infusion of arsenic trioxide however it is preferred for blood work
- Dosing of arsenic trioxide based on total body weight in obese patients may result in higher than expected plasma and tissue concentrations. Monitor all obese patients closely for signs of acute arsenic toxicity
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively
- **Renal dysfunction:** patients with creatinine clearance less than 30 mL/minute may require dose reduction
- **Acute arsenic toxicity** may present as convulsions, muscle weakness, confusion and EKG abnormalities
- **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 twice daily should be initiated
- **Leukocytosis** may develop after treatment initiation. Patients can be treated with hydroxyurea 500 mg orally four times daily for WBC  $10\text{-}50 \times 10^9/\text{L}$  or 1000 mg orally four times daily for WBC greater than  $50 \times 10^9/\text{L}$ . Discontinue hydroxyurea when WBC is less than  $10 \times 10^9/\text{L}$
- **Transient, mild headache** may occur several hours after ATRA ingestion
- **Hypervitaminosis A syndrome** has been observed with ATRA, and may include xeroderma, lip and mouth dryness, cheilitis, rash, edema, nausea, vomiting and bone pain
- **Benign or idiopathic intracranial hypertension** (pseudotumour cerebri) may occur with an onset of about 3-17 days of ATRA therapy
- **Venous and arterial thrombosis** is a risk during the first month of ATRA treatment
- **Hepatitis B Reactivation:** All patients should be tested for HBsAg and HBcAb. If either test is positive, such patients should be treated with tenofovir 300 mg/day orally for the entire duration of the chemotherapy and for six months afterwards. The patients should also be monitored with frequent liver enzymes 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
- VESANOID® (ATRA) will be dispensed by CCMB Pharmacy

### Appendix A

#### Consolidation dosing schema (low risk or intermediate risk group)

##### Cycles 1, 3, 5, 7

| Day   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |  |
|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| arsenic trioxide 0.15 mg/kg IV daily                                  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| VESANOID® (ATRA) 45 mg/m <sup>2</sup> /day orally divided twice daily |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |

##### Cycles 2, 4, 6

| Day   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |  |
|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| arsenic trioxide 0.15 mg/kg IV daily                                  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| VESANOID® (ATRA) 45 mg/m <sup>2</sup> /day orally divided twice daily |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |

Key: ■ indicates that this medication will be administered on this day