Regimen Reference Order

LEUK – APML4 Consolidation Cycle 2 (APL)

ARIA: LEUK - [APML4 Consolidation 2]

Planned Course: 1 Cycle (1 cycle = 35 days)
Indication for Use: Acute Promyelocytic Leukemia; High Risk

CVAD: At Provider's Discretion

Proceed with treatment if:

Day 1

- ***ANC equal to or greater than 1.5 x 10^9/L AND Platelets equal to or greater than 100 x 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***
  - ❖ **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 – APML4 Consolidation Cycle 2 (APL)

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
Consolidation Cycle 2 starts 3 to 4 weeks after completion of LEUK – APML4 Consolidation Cycle 1 (APL)		
VESANOID® (ATRA)	45 mg/m^2/day (to nearest 10 mg)	Orally divided twice daily on **Days 1 to 7, 15 to 21, 29 to 35** Take with food. Swallow whole **(Self-administered at home)**
Days 1 to 5		
arsenic trioxide	0.15 mg/kg	IV in normal saline 100 mL over 2 hours
Days 8 to 12		
arsenic trioxide	0.15 mg/kg	IV in normal saline 100 mL over 2 hours

Days 15 to 19		
arsenic trioxide	0.15 mg/kg	IV in normal saline 100 mL over 2 hours
Days 22 to 26		
arsenic trioxide	0.15 mg/kg	IV in normal saline 100 mL over 2 hours
Days 29 to 33		
arsenic trioxide	0.15 mg/kg	IV in normal saline 100 mL over 2 hours
****See Appendix A – Consolidation Cycle 2 (high risk group) dosing schema***		
all-trans retinoic acid (VESANOID®) available dosage strength: 10 mg capsule **Classification: Non-Cytotoxic, Hazardous** ******* Note: ATRA = all-trans retinoic acid = tretinoin = VESANOID® ******* ***Not to be confused with isotretinoin (ACCUTANE®, EPURIS® or CLARUS®)***		

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

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_2 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

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
valACYclovir	500 mg	Orally twice daily

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
- Remind patient to take valACYclovir (shingles prophylaxis) at home
- 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 10-50 x 10^9/L or 1000 mg orally four times daily for WBC greater than 50 x 10^9/L. Discontinue hydroxyurea when WBC is less than 10 x 10^9/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
- Upon completion of **LEUK – [APML4 Consolidation 2]**, patients should be started on **LEUK – [APML4 Maintenance]**
    - **LEUK – [APML4 Maintenance]** regimen starts 3 to 4 weeks after completing **LEUK – [APML4 Consolidation 2]**

Appendix A

Consolidation - Cycle 2 (high risk group) dosing schema

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	29	30	31	32	33	34	35
arsenic trioxide 0.15 mg/kg IV daily	■	■	■	■	■			■	■	■	■	■			■	■	■	■	■			■	■	■	■	■			■	■	■	■	■		
VESANOID® (ATRA) 45 mg/m²/day orally divided twice daily	■	■	■	■	■	■	■								■	■	■	■	■	■	■								■	■	■	■	■	■	■

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