Induction therapy with All-trans retinoic acid (ATRA) and Arsenic trioxide for Acute Promyelocytic Leukemia

Contact Physician:_____ Pager: _____

Diagnosis:_____

Day 1 = _____ Cycle 1: consent form done ☐

Weight:_____ **Height**:_____ **BSA**:_____

Adjusted IBW:_____ **Adjusted BSA**:_____

Allergies:_____

Low risk: WBC <10,000
All-trans retinoic acid (ATRA) 45mg/m²/day PO in 2 divided doses starting day 1 and continue until HCR or maximum of 90 days.
Arsenic trioxide 0.15mg/kg IV daily over one hour starting day 10 and continue until HCR or until day 85 from start of therapy.

High risk: WBC>10,000
All-trans retinoic acid (ATRA) 45mg/m²/day PO in 2 divided doses starting day 1 and continue until CR or maximum of 90 days.
Arsenic trioxide 0.15mg/kg IV daily over one hour starting day 10 and continue until CR or until day 85 from start of therapy.
Gemtuzumab ozogamycin 9mg/m² IV day 1

Hematologic CR= ANC>1000 and platelet > 100,000 with noted marrow findings.
For patients ≤ 20 years of age, dose reduce ATRA to 25mg/m²/day

1. **Hydration:** Sodium chloride 0.9% IV at 100ml/hr continuously

2. **Prophylactic medications:**
   - ☐ Allopurinol: 300mg PO daily for _____ days
   - ☐ Acyclovir: 400mg PO twice daily
   - ☐ Antifungal:
   - ☐ GI prophylaxis:

3. Anti-emetics: (check the appropriate medications)

- ☐ Lorazepam: 0.5mg - 1 mg PO or IV every 4 hours prn nausea
- ☐ Prochlorperazine 10mg PO every 6 hours prn nausea

4. Chemotherapy: Select Low risk or High risk

☐ **LOW RISK:** WBC <10,000

- **All-trans retinoic acid (**45mg/m²/day) _____mg PO in two divided doses rounded to the nearest 10mg, _____mg in morning and _____mg in evening starting day 1____. Continue daily for a maximum of 90 days. Tablet size: 10mg (For patients < 20years of age, dose reduce ATRA to 25mg/m^2/day)

- **Arsenic trioxide** (0.15mg/kg) _____mg in Sodium Chloride 0.9% 250mL IV over one hour daily starting day 10_____. Continue until CR or until day 85 from start of therapy. (Alternate: May consider giving 5 days/week; Mon-Fri)
  Arsenic trioxide _____ mg IV over one hour on _____.
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  Arsenic trioxide _____ mg IV over one hour on _____.

□ **HIGH RISK:** WBC>10,000

- **All-trans retinoic acid (**45mg/m²/day) _____mg PO in two divided doses rounded to the nearest 10mg, _____mg in morning and _____mg in evening starting day 1____. Continue daily for a maximum of 90 days. Tablet size: 10mg

- **Arsenic trioxide** (0.15mg/kg) _____mg in Sodium Chloride 0.9% 250mL IV over one hour daily starting day 10_____. Continue until CR or until day 85 from start of therapy. (Alternate: May consider giving 5 days/week; Mon-Fri) (For patients ≤20years of age, dose reduce to 25mg/m^2/day)
  Arsenic trioxide _____ mg IV over one hour on _____.
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  Arsenic trioxide _____ mg IV over one hour on _____.
  Arsenic trioxide _____ mg IV over one hour on _____.

- **Gemtuzumab ozogamycin**

  □ **Gemtuzumab ozogamycin** (9mg/m²) _____ mg IV in Sodium Chloride 0.9% 100mL over 2 hours on day 1_____. Infuse gemtuzumab through a separate IV line with low protein-binding 0.22 micron terminal filter.
  Premedicate with:
  □ **Diphenhydramine** 50mg PO one hour prior to gemtuzumab ozogamicin and 4 and 8 hours post gemtuzumab ozogamicin
  □ **Methylprednisolone** 50mg IV one hour prior to and one hour into the infusion of gemtuzumab ozogamicin
  □ **Acetaminophen** 650mg PO one hour prior to gemtuzumab

5. APL Differentiation Syndrome (APLDS):

- Notify Hematology team for any signs/symptoms of APLDS
- Consider APLDS when: unexplained fever, weight gain, serous effusions (pleural, pericardial), pulmonary infiltrates, peripheral edema, hypotension/orthostasis, rapidly increasing WBC.
- For changes consistent with APLDS, treat with Dexamethasone 10mg IV twice daily until symptoms resolve. Consider holding ATRA/Arsenic and resume upon resolution of symptoms. Based on severity of APLDS, may consider resuming medications at lower dose and in 3-5 days increase to full dose if no recurrence of APLDS.

6. Coagulopathy:

- See lab monitoring and treatment guidelines under Hematology protocols; Treatment of Acute Promyelocytic Leukemia.

7. APL Monitoring

- Consider bone marrow aspirate around day 28 from start of treatment or when peripheral counts suggest remission.

Signed:_____ Pager:_____

Blood 2006: 107 (9) 3469-3473.

<u>Addendum: Recommended monitoring and dose reductions</u>

All trans retinoic acid*:*

- For grades 3&4 toxicity (headaches, rash) reduce dose by 50%. Discontinue if toxicity persists after dose reduction.

Arsenic trioxide:

Dose reductions:

- For peripheral neuropathy or arrhythmias, dose reduce or discontinue.
- Signs and symptoms of toxicity (convulsions, muscle weakness, confusion) require immediate discontinuation of arsenic trioxide therapy and consideration of chelation therapy (dimercaprol 3mg/kg

intramuscularly every 4 hours until life threatening toxicity has subsided and may be followed by penicillamine 250mg orally up to 4 times daily).

Monitoring parameters:

- Prior to initiating therapy serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; pre-existing abnormalities should be corrected
- Prior to initiating therapy, a 12 lead electrocardiogram (ECG) should be performed. QT intervals greater than 500milliseconds should be corrected and reassessed with serial ECGs prior to considering therapy.
- During therapy, hematologic, electrolyte, and coagulation profiles should be monitored twice weekly during the induction phase (more frequently for clinically unstable patients) and at least weekly during the consolidation phase. Potassium concentrations should be kept above 4mEq/dL and magnesium concentrations should be kept above 1.8mEq/dL.
- During induction and consolidation, ECGs should be obtained weekly (more frequently for clinically unstable patients). Patients with QT intervals that exceed 500milliseconds during therapy require action to correct concomitant risk factors and assessment of risk/benefit of continuing therapy.

Reference: Product information