1 Acute Promyelocytic Leukaemia

1.34 Arsenic Trioxide + ATRA – Clinical Trial AML17

Indication
- Induction and Consolidation of APL – Arm B of AML 17 Clinical Trial

Pre-treatment Evaluation
- Morphology of blood and bone marrow aspirate.
- Trephine biopsy and ‘roll preparations’ should be made if the aspirate is difficult
- 6ml bone marrow or 30ml peripheral blood in EDTA to be collected from trial patients and sent by courier to Haematology Department at Royal Free Hospital.
- Cytochemistry: myeloperoxidase, PAS, acid phosphatase – note this may not be done routinely in some labs where immunophenotyping is readily available.
- Trial patients should have 4ml bone marrow in tissue culture medium with preservative free heparin/ 30ml of heparinised blood sent to local lab for cytogenetic analysis. FISH analysis for common translocations and mono/trisomies may be useful.
- Molecular analysis for relevant chimaeric genes, especially PML/RARA, BCR-ABL and (AML/ETO if available). Trial patients should have 4ml of bone marrow in culture medium, and 30ml heparinised blood sent to Guy’s St Thomas Hospital.
- Lumbar puncture (glucose, protein, microbiological culture, cytospin, gene rearrangement studies). This is not performed unless clinical suspicion of CNS disease.
- Serological tests for: Hepatitis B & C, CMV, and HIV (with consent).
- CXR.
- ECHO/ MUGA if cardiac history, elderly or previous history suggestive of potential cardiac disease (inc diabetes and hypertension)
- ECG assessment before and up to twice weekly during treatment to ensure that the QT interval does not exceed 460 msec. Drugs which can prolong the QT interval should be avoided. (For a list of such drugs visit www.torsades.org).
- Clotting screen.
- FBC and blood film.
- Renal/liver/bone panel, LDH, CRP, uric acid, serum glucose and blood cholesterol level.
- Ensure the serum potassium is kept above 4mmol/l and the serum magnesium above 1.8mg/d to minimise the risk of severe arrhythmias, particularly in patients receiving concomitant drugs that induce hypokalemia or hypomagnesemia
- Daily Weight
- Document height, weight and body surface area.
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects.
- Obtain written consent from patient or guardian.
If appropriate, discuss the possibility of pregnancy with female patients of childbearing age and the need for contraception with both male and female patients. Women of child-bearing potential must have a negative pregnancy test within 2 weeks of trial entry.

If appropriate, discuss potential risk of infertility with patient and relatives. Sperm banking if appropriate and time allows.

Retinoic acid syndrome (or ATRA syndrome) includes fever, dyspnoea, respiratory distress, hypotension, oedema, pleural or pericardial effusion, hepatic, renal and multi-organ failure. It is frequently associated with a raised WBC and may be fatal. If the patient presents any signs of this syndrome (eg unexplained respiratory distress):

1. Immediately discontinue tretinoin until clinical condition improves.
2. Initiate dexamethasone 10mg every 12 hours for up to maximum of 3 days or until resolution of the symptoms.
3. Furosemide may be clinically require
4. Within 4 days of disappearance of symptoms, re-introduce tretinoin at 50% dose. In absence of return of symptoms, full dose may then be resumed. If symptoms do return, tretinoin should be discontinued permanently. Pseudotumour cerebri, defined as severe headache with nausea, vomiting and visual disorders, may occur with retinoin. It may be necessary to temporarily discontinue retinoin and treat with opiates. In such a case, within 4 days of disappearance of symptoms, re-introduce tretinoin at 50% dose. In absence of return of symptoms, full dose may then be resumed.

### Drug Regimen

#### 1. Induction

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 until Complete Remission or</td>
<td>Tretinoin (ATRA)</td>
<td>45 mg/m²/day</td>
<td>Orally in TWO equally divided doses</td>
<td>Rounded to the nearest 10 mg increment</td>
</tr>
<tr>
<td>up to 60 days whichever is earlier</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1 to 5 then twice weekly for an</td>
<td>Arsenic Trioxide</td>
<td>0.30mg/kg/day for 5</td>
<td>IV infusion in 100-250 ml of glucose 5% or sodium chloride 0.9% over 2 hours</td>
<td></td>
</tr>
<tr>
<td>addition of 7 weeks</td>
<td>(ATO)</td>
<td>doses then 0.25mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>twice weekly for 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comment:** Patients should have a bone marrow re-assessment at 30 days which should include molecular assessment. Patients should enter consolidation treatment if they are in complete remission which is defined as the bone marrow is regenerating normal haemopoietic cells and contains <5% blast cells by morphology in an aspirate sample with at least 200 nucleated cells. Additionally there is an absolute neutrophil count of more than 1000/µL and platelet count of at least 100,000/µL. If haematologic Complete Remission is not achieved by 60 days after start of induction, patient will go off-study.
2. **Consolidation**

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks on followed by 2 weeks off, for a total of 7 cycles</td>
<td>Tretinoin (ATRA)</td>
<td>45 mg/m²/day</td>
<td>Orally in TWO equally divided doses</td>
<td>Rounded to the nearest 10 mg increment</td>
</tr>
<tr>
<td>D1 to 5 then twice weekly for 3 weeks followed by 4 weeks rest</td>
<td>Arsenic Trioxide (ATO)</td>
<td>0.30mg/kg/day for 5 doses <em>then</em> 0.25mg/kg twice weekly for 3 weeks</td>
<td>IV infusion in 100-250 ml of sodium chloride 0.9% over 2 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Comment:** Marrow samples will be collected at day 60 and after the end of consolidation cycles of ATO, to be tested by RQ-PCR for assessment of molecular remission. Patients who do not achieve molecular remission by the end of the 3rd consolidation cycle will be considered as molecular resistant and will go off study. Marrow samples collected at earlier time points are used to measure disease response and provide early indication of patients at risk of failing first line therapy.

If the patient has achieved a molecular remission arrangements should be made to undertake autologous stem cell transplant. Patients who remain in remission but are molecularly positive should be assessed for allogeneic stem cell transplant. If no transplant option is available the patient should commence maintenance chemotherapy.

**Cycle Frequency / Duration**
This will be repeated for a total of 4 cycles

**Dose Modifications**

### Renal Impairment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>Limited information – SPC advises that the dose be decreased to 25mg/m² as a precautionary measure.</td>
</tr>
<tr>
<td>Arsenic Trioxide</td>
<td>Limited information</td>
</tr>
</tbody>
</table>

### Liver Impairment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>If serum bilirubin, transaminases or ALP &gt; 5 x ULN, tretinoin should be temporarily withheld. Once serum bilirubin, transaminases or ALP &lt; 4 x ULN, tretinoin may be resumed at 50% dose. If liver enzymes do not worsen after a trial period at this dose, full dose tretinoin may be resumed. Monitor with care</td>
</tr>
<tr>
<td>Arsenic Trioxide</td>
<td>Limited information</td>
</tr>
</tbody>
</table>
Concurrent Medication

- Adequate hydration, potassium and magnesium supplements to maintain serum potassium above 4mmol/l and serum magnesium above 1.8mg/dl.
- Allopurinol should be given as soon as possible after diagnosis at a daily oral dose of 300 mg daily (adjusted as above for renal failure). Patients with high counts at diagnosis or an allergy to allopurinol can be considered for treatment with Rasburicase to reduce the effect of tumour lysis at induction.
- Anti-ulcer drug as per local policy

Anti-emetics

ARSENIC TRIOXIDE has low emetic protential – follow local protocol

Adverse effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>The most common adverse effect of ATRA has been headaches of mild to moderate severity. Bone pain, occasionally requiring analgesic treatment, has also been observed. Biochemical abnormality of liver function has occasionally been reported, specifically raised transaminases, alkaline phosphatase and bilirubin, but these are reversible on stopping the drug. The most serious adverse event has been a syndrome characterised by fever, respiratory distress and episodic hypotension, usually in association with leucocytosis (now known as “Differentiation Syndrome”). The onset of this syndrome has usually been in the first 1-2 weeks of drug treatment. Should this occur the ATRA should be stopped and steroids commenced as detailed above. Some cases are reported to respond well to high-dose corticosteroid therapy (dexamethasone 10 mg i.v. 12 hourly for 3 or more days). Prolonged ATRA treatment may cause dryness of the skin and other dermatological side effects, like erythema, rash, pruritus, alopecia, hyperhidrosis. ATRA is also believed to be highly teratogenic and advice regarding contraception should be given as appropriate.</td>
</tr>
<tr>
<td>Arsenic Trioxide</td>
<td>The main adverse events expected during the induction cycle are often related to APL Differentiation Syndrome. Common side effects: Bone pain, arthralgia, neutropenia, thrombocytopenia, hyperglycaemia, hypokalaemia, hypomagnesaemia, paraesthesia, pleuritic pain, dyspnoea, pyrexia, fatigue, ECG QT prolonged, increased ALT, aspartate amino transferase and hyperbilirubinaemia.</td>
</tr>
</tbody>
</table>

References

* AML 17 – MRC Protocol (May 2008)
* [emc.medicines.org.uk](http://emc.medicines.org.uk)

Patient information

* Leukaemia Research Fund - Adult Acute Myeloid Leukaemia booklet
* CancerBACUP - Acute myeloid leukaemia booklet