1 Acute Myeloid Leukaemia

1.17 Idarubicin

Pre-treatment Evaluation

- Morphology of blood and bone marrow aspirate. Trial patients: send 6 unstained slides to Leeds General Infirmary.
- Trephine biopsy and ‘roll preparations’ should be made if the aspirate is difficult.
- Immunophenotyping (including TdT, B & T markers, myeloid markers, cytoplasmic μ, surface Ig), preferably on bone marrow (BM) or peripheral blood (PB) blasts. For trial patients immunophenotyping is performed in the Haematology Department at the Royal Marsden Hospital. Samples should be sent by courier.
- Cytochemistry: myeloperoxidase, PAS, acid phosphatase (if T-cell suspected) – note this may not be done routinely in some labs where immunophenotyping is readily available.
- Cytogenetic analysis, usually on bone marrow. FISH analysis for common translocations and mono/trisomies may be useful.
- Molecular analysis for relevant chimaeric genes, especially PML/RARA, RAR-PML. Trial patients should have 4ml of bone marrow in culture medium, and 30ml heparinised blood sent to UCH.
- 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.
- ECG.
- ECHO if cardiac history, elderly or previous history suggestive of potential cardiac disease (Inc diabetes and hypertension).
- Clotting screen.
- FBC and blood film.
- Renal/liver/bone panel, LDH, CRP, uric acid, serum glucose.
- Document WHO performance status of patient...
- 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 child-bearing age and the need for contraception with both male and female patients.
- If appropriate, discuss potential risk of infertility with patient and relatives.
- Central venous catheter insertion.
- Due to an increased risk if bleeding diathesis/DIC at diagnosis and during induction treatment. Ensure the patient’s platelet count is maintained above 30x10^9/L and fibrinogen level above >2g/L with normal PT/aPTT by treatment with appropriate therapeutic agents. If bleeding occurs (discuss with doctor in charge) this is a medical emergency and ATRA should be initiated urgently whilst haematological transfusion support is given.
### Drug Regimen – Spanish Approach - Course 1, (OPCS code: X71.5)

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2, 4, 6 &amp; 8 (4doses)</td>
<td>Idarubicin</td>
<td>12mg/m&lt;sup&gt;2&lt;/sup&gt; daily</td>
<td>IV slow bolus in free running Sodium Chloride 0.9% drip over 10 min</td>
<td>Patients who present with a WBC &gt; 10 x 10&lt;sup&gt;9&lt;/sup&gt;/l should receive Dexamethasone 10 mg IV. BD for days 1-5 as prophylaxis against retinoic acid syndrome. Heparin &amp; Tranexamic Acid should not be routinely used.</td>
</tr>
<tr>
<td>D1 to first CR or until completion of 2 courses of chemotherapy</td>
<td>Tretinoin (ATRA)</td>
<td>45mg/m&lt;sup&gt;2&lt;/sup&gt; daily (round to nearest 10mg)</td>
<td>oral</td>
<td></td>
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</table>

### Drug Regimen – Spanish Approach - Course 2 (OPCS code: X71.2)

<table>
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<th>Days</th>
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<th>Dose</th>
<th>Administration</th>
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</thead>
<tbody>
<tr>
<td>D1- 4 inclusive (4doses)</td>
<td>Idarubicin</td>
<td>7mg/m&lt;sup&gt;2&lt;/sup&gt; daily</td>
<td>IV slow bolus in free running Sodium Chloride 0.9% drip over 5-10 min</td>
</tr>
<tr>
<td>D1 to 15 inc. (15doses) if in CR or until completion of 2 courses of chemotherapy</td>
<td>Tretinoin (ATRA)</td>
<td>45 mg/m&lt;sup&gt;2&lt;/sup&gt; daily (round to nearest 10mg)</td>
<td>oral</td>
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**Note - Spanish Approach - Course 3** consists of Mitozantrone and ATRA + Gemtuzumab see protocol 1.20 (OPCS code: X70.4)

### Drug Regimen – Spanish Approach - Course 4 (OPCS code: X70.4)

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
</tr>
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<tbody>
<tr>
<td>D1 (1dose)</td>
<td>Idarubicin</td>
<td>12mg/m&lt;sup&gt;2&lt;/sup&gt; daily</td>
<td>IV slow bolus in free running Sodium Chloride 0.9% drip over 5-10 min</td>
</tr>
<tr>
<td>D1-15 inc. (15doses)</td>
<td>Tretinoin (ATRA)</td>
<td>45 mg/m&lt;sup&gt;2&lt;/sup&gt; daily (round to nearest 10mg)</td>
<td>oral</td>
</tr>
</tbody>
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**Cycle Frequency**

No information

**Dose Modifications**

<table>
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<tr>
<th>Creatinine Clearance</th>
<th>Idarubicin</th>
<th>Tretinoin</th>
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</thead>
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<tr>
<td>30-60ml/min</td>
<td>50%</td>
<td>consider a dose reduction to</td>
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*CR – defined as molecular/cytogenetic*
Serum Bilirubin† | Idarubicin Dose | Tretinoin
--- | --- | ---
21 – 34µmol/L | 50% dose | consider a dose reduction to 25mg/m²
>34µmol/L | clinical decision | 

**Investigations prior to subsequent cycles**

- Clotting screen.
- FBC and blood film.
- Renal/liver/bone panel, LDH, CRP, uric acid, serum glucose.
- for AML intensive treatment patients, at day 18-21 after the end on Course 1 a bone marrow aspirate & trephine biopsy, and as clinically indicated with recover of counts (to assess remission status and risk).
- It is recommended that patients be allowed to regenerate to 1.0 x 10^9/l neutrophils and 100 x 10^9/l platelets before starting the second course of chemotherapy.

**Treatment Duration**

No information

**Concurrent Medication**

- Adequate hydration, if tumour lysis is expected, add 50mmol Sodium Bicarbonate per litre hydration fluid. Adjust the sodium bicarbonate concentration to maintain the urinary pH between 7 and 8 (i.e. alkaline).
- 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) and continued until at least day 29 of the first phase of chemotherapy. (See information on phase 2). 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. On subsequent cycles, clinical decision.
- Anti-ulcer drug as per local policy.
- Dexamethasone can be given when prescribing ATRA to reduce effects of ATRA Syndrome if clinically indicated (see adverse reactions).
- Antimicrobial and antifungal prophylaxis as per local protocol.
- Consider the use of an emollient

**Anti-emetics – moderate emetogenic protocol**

- Pre-Chemo
  - Granisetron 1mg IV stat or 2mg PO stat or Ondansetron 8mg IV stat
- Post-Chemo
  - Metoclopramide 20mg TDS PO 3- 5 days or Domperidone 20mg TDS PO for 3-5 days

**Adverse effects**

† Note if raised bilirubin is not caused by hepatic dysfunction, DO NOT alter the dose
• Idarubicin adverse effects: The major effect is myelosuppression. Cardiac toxicity may occur, manifested by cardiac failure, arrhythmias or cardiomyopathies, either during therapy or several weeks later. The cumulative dose associated with cardiotoxicity is not known, but it is believed that a total dose of 60-80 mg/m\(^2\), which is considerably higher than that used in AML12, is not problematic. Idarubicin may cause a red discoloration of the urine for 1-2 days after administration. Reversible alopecia will occur, and some nausea or vomiting and oral mucositis should be expected. Elevation of liver enzymes and bilirubin may occur in a minority of patients.

• The most common adverse effect of ATRA has been headache of mild to moderate severity. Younger (paediatric) patients appear to be more sensitive to this particular effect. Bone pain, occasionally requiring analgesic treatment, has also been observed. The major adverse effects to be aware of are:

**ATRA Syndrome**
This is accurately defined by the presence of: unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusion, with or without hyperleukocytosis. No single sign or symptom itself may be considered diagnostic of the syndrome. However, at the earliest manifestations of suspected ATRA Syndrome (e.g. unexplained respiratory distress), and prior to development of a full blown syndrome, the following measures should be immediately undertaken:

- temporary discontinuation of ATRA treatment.
- prompt initiation of DEXAMETHASONE, 10 mg IV, 12-hourly until disappearance of symptoms and signs, and for a minimum of 3 days.
- frusemide when clinically required.

**Pseudotumour Cerebri**
This is defined as presence of: severe headaches with nausea, vomiting, and visual disorders. In this case, generally developing in patients under 20 years of age, it is often necessary to temporarily discontinue ATRA treatment and to administer opiates.

**Hepatotoxicity**
This is defined as: an increase in serum bilirubin, AST/ALT, or alkaline phosphatase >5 times the normal upper level. This requires a temporary suspension of the ATRA. The Idarubicin doses should not be changed if on the Spanish schedule. As soon as the symptoms and the patient's clinical condition improves, treatment with ATRA will be resumed at 50% of the previous dose during the first 4 days after the disappearance of retinoic acid syndrome, amelioration of pseudotumour cerebri or when serum bilirubin, AST/ALT or alkaline phosphates are reduced to <4 times the normal upper level. Thereafter, in absence of worsening of the previous toxicity, ATRA should be resumed at full dosage. In case of reappearance of signs and symptoms of ATRA toxicity, the drug must be discontinued indefinitely during induction therapy. However, patients who enter the maintenance phase of the Spanish schedule should receive ATRA where possible.

**References**

- AML 15 – MRC Protocol (January 2005)
- [emc.medicines.org.uk](http://emc.medicines.org.uk)
• NLCN Dosage Adjustment for Cytotoxics in Hepatic Impairment, November 2003
• NLCN Dosage Adjustment for Cytotoxics in Renal Impairment, November 2003

**Patient information**
• Leukaemia Research Fund - Adult Acute Myeloid Leukaemia booklet
• CancerBACUP - Acute myeloid leukaemia booklet
• Cancer BACUP fact file – patient drug information leaflets

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<tr>
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