ATRA & ARSENIC TRIOXIDE

INDICATIONS: Treatment of high risk acute promyelocytic leukaemia – haematological or molecular relapse, and molecular persistence following chemotherapy.

Initial treatment for patients with APML where Spanish AIDA treatment is contra-indicated

Prior to a course of treatment

- Check FBC, coagulation, U&Es, creat, LFTs, glucose, baseline weight, CXR & ECG
- Use with caution if pre-existing renal or hepatic dysfunction – *discuss with consultant*
- Correct any electrolyte disturbances – **K^+ must be >4.0mmol/l, Mg^{++} > 0.74mmol/l**
- Baseline ECG – QTC must be <500msec – if not *discuss with consultant*
- Admit for 1st week - consider cardiac monitoring if risk factors for QTC prolongation or torsades
- Review and consider discontinuing any medications known to produce torsades de pointes (*amiodarone, clarithromycin, chlorpromazine, chloroquine, domperidone, erythromycin, haloperidol , methadone, pentamidine, sotalol, and see http://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf for a list)*
- Can be given either through central or peripheral venous line
- Consider analysis of CSF if relapsed APML (high incidence of occult disease)

INDUCTION

ATRA	ATRA 45mg/m^2 /day PO as two equally divided doses until CR (round to nearest 10mg). **–** Prescribe as Tretinoin		
Arsenic Trioxide	0.3mg/kg daily	IV in 250ml N saline over 2 hrs	Days 1-5
	0.25mg/kg	IV in 250ml N saline over 2hrs	Twice a week for an additional 7 weeks

Patients who present with WCC >10 have a higher chance of differentiation syndrome if allocated ATRA + Arsenic. When this treatment used to be part of the AML17 trial, these patients received Mylotarg 3mg/m^2 on day 1of treatment & on day 4 if the WCC has not fallen below 10. It may or may not be possible to obtain Mylotarg outside of a clinical trial in this situation but *discuss with consultant*

Important points about Mylotarg:

- Liver function tests should show ALT ≤ 2.5 x ULN, bilirubin ≤ 2x ULN
- Paracetamol & azole prophylaxis should be avoided in the first week after Mylotarg
- Liver function should be monitored for 10 – 14 days following Mylotarg. Patients should be monitored for potential veno-occlusive diease, characterised by weight gain, painful hepatomegaly & ascites.

CONSOLIDATION treatment is for 28 weeks

ATRA	ATRA 45mg/m^2 /day PO as two equally divided doses (round to nearest 10mg) Give 2 weeks on followed by 2 weeks off, for a total of 7 cycles (last cycle administered on weeks 25-26). Prescribe as Tretinoin
Arsenic Trioxide	0.3mg/kg IV in 250 mls N saline over 2 hours daily for 5 days in week 1 Weeks 2 – 4: 0.25mg/kg in 250 mls N saline over 2 hours twice per week, followed by 4 weeks with no treatment Repeat for a total of 4 cycles (last cycle administered on weeks 25-28)

During a course of treatment
• Check FBC, Coagulation, U&Es, creat, LFTs, glucose at least twice weekly and more frequently if there is any disturbance. Correct electrolytes to maintain K >4.0mmol/l, Mg > 0.74mmol/l
• Note that drugs commonly used in haematology may prolong the QT interval and should be avoided when Arsenic is being used. These include ondanestron, ciprofloxacin and azole anti-fungals.
• Discuss with consultant if there is deterioration in renal or liver function.
• Advise patient to immediately report any syncope, rapid heart beat
• ECG at least twice a week and more frequently if symptomatic. If QTC >500msec, reassess, review medications and electrolytes as above. Consider hospitalisation and cardiac monitoring – discuss with consultant. Suspend arsenic until electrolytes corrected & symptoms & ECG changes resolve.
• Advise patient to immediately report fever, sudden weight gain, fluid retention, musculoskeletal pain or dyspnoea. This may reflect onset of differentiation syndrome – check ABGs, CXR & initiate dexamethasone 10mg IV bd for at least 3 days after discussion with consultant.

Arsenic / ATRA Consolidation Treatment on AML17

Week		**Date**		
1	Monday		ATRA	5 days arsenic
2	Monday		ATRA	2 days arsenic
3	Monday			2 days arsenic
4	Monday			2 days arsenic
5	Monday		ATRA	
6	Monday		ATRA	
7	Monday			
8	Monday			
9	Monday		ATRA	5 days arsenic
10	Monday		ATRA	2 days arsenic
11	Monday			2 days arsenic
12	Monday			2 days arsenic
13	Monday		ATRA	
14	Monday		ATRA	
15	Monday			
16	Monday			
17	Monday		ATRA	5 days arsenic
18	Monday		ATRA	2 days arsenic
19	Monday			2 days arsenic
20	Monday			2 days arsenic
21	Monday		ATRA	
22	Monday		ATRA	
23	Monday			
24	Monday			
25	Monday		ATRA	5 days arsenic
26	Monday		ATRA	2 days arsenic
27	Monday			2 days arsenic
28	Monday			2 days arsenic

Arsenic Trioxide Toxicities

Prolongation of QT interval, torsade de pointes, atrial flutter/fibrillation, syncope & cardiac arrest

Electrolyte disturbance – hypokalaemia, hypomagnesaemia (*see During a course of treament*)

Infusion-related vasomotor symptoms – tachycardia, hypotension, flushing, headache, dizziness

Hyperleucocytosis & differentiation syndrome (*see During a course of treament*)

Headache

Arthralgia

Abnormal LFTs - transaminitis	Fatigue
Hyperglycaemia	Fever

Retinoic acid (differentiation) syndrome

- This is a major cause of mortality in patients treated with ATRA. The patient may have unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusions. Usually there is also hyperleucocytosis but the syndrome may occur at any level of WBC.
- At the earliest suspicion of the ATRA syndrome *discuss the case with the consultant*. Administer dexamethasone 10mg 12-hourly IV until disappearance of symptoms and signs and for a minimum of 3 days. The decision to continue or discontinue ATRA depends on the severity of the differentiation syndrome and this should be made by a consultant.

Pseudotumour cerebri

- This may develop in patients under 20years of age. It presents with headaches, nausea, vomiting and visual disturbances. *Discuss with the consultant* and temporarily stop ATRA.

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.
- If hepatoxicity persists following discontinuation of ATRA, the Idarubicin doses should not be changed on the AIDA arm.
- 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 when serum bilirubin, AST/ALT or alkaline phosphatase 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.

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