Thames Valley
Strategic Clinical Network

ATRA + ARSENIC TRIOXIDE

INDICATION

Induction of remission and consolidation in adult patients with

- newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (white blood cell count ≤10x10^9/L) in combination with all-trans-retinoic acid (ATRA)
- relapsed/refractory APML (previous treatment should have included a retinoid and chemotherapy)

characterised by the presence of the t(15;17) translocation and/or the presence of the PML/RAR-alpha gene. **(NICE TA526- BLUETEQ required)**

NB: OUH has opted to follow the arsenic trioxide schedule in the AML17 trial which is different to the product license in both newly diagnosed and R/R settings. ATRA+ Arsenic trioxide combination in R/R setting is unlicensed in the UK. Local unlicensed medication policy should be followed in these situations.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen including fibrinogen and D-dimers, DAT, U&Es, eGFR, urate, calcium, magnesium, creatinine, LFTs, glucose, Hepatitis B core antibody and Hepatitis B surface antigen, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save
2. **Tests and treatment of APL coagulopathy** – APTT, prothrombin time, thrombin time, fibrinogen level and platelet count should be checked at least twice daily during the early stages of treatment. Coagulation times should be kept within the normal range using FFP replacement. Fibrinogen levels may be low due to DIC and cryoprecipitate should be given as replacement aiming for a level of approximately 2 g/L. Elevated levels of fibrinogen should be avoided because of the increased risk of thrombosis associated with APL, which may be further exacerbated by ATRA. The platelet count should ideally be maintained above 50 × 10^9/L until morphological remission has been confirmed. Thereafter, check PT, APTT and Fibrinogen daily until morphological remission.
3. Ensure the serum potassium is kept above 4mmol/L and the serum magnesium above 0.7mmol/L to minimise the risk of severe arrhythmias, particularly in patients receiving concomitant drugs that induce hypokalemia or hypomagnesemia
4. ECG and Echo within a week of starting (do not wait for results), then ECG assessment before and up to twice weekly during treatment with Arsenic Trioxide to ensure that the QT interval does not exceed 460 msec. Drugs which can prolong the QT interval should be avoided (see below).
5. Ensure diagnosis is confirmed (including cytogenetic and/ or molecular testing) prior to administration of chemotherapy and document in notes. In some cases of rapidly progressing disease, ATRA treatment may need to be started before de facto confirmation

of diagnosis is made.

6. Pregnancy Test - for all women with childbearing potential before each new chemotherapy course.
7. Record performance status (WHO/ECOG)
8. Record height and weight
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment
10. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice.
11. Hydration - in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Refer to local tumour lysis prophylaxis protocol for high risk patients.
12. Consider dental assessment / advise dental check is carried out by patient's own dental practitioner before treatment starts
13. Treatment should be discussed and agreed (can be retrospective) in the relevant MDT
14. Patients who present with a WBC >10 x 10^9/L have a higher chance of developing differentiation syndrome (DS). Consider prophylactic corticosteroids (e.g. dexamethasone 10mg bd) with patients with WBC >10x10^9/L and other high risk features e.g. renal failure. Once DS is suspected, stop ATRA and Arsenic Trioxide, give dexamethasone (10mg bd IV) until symptoms resolve (see below).
15. Patients must be hospitalised at the beginning of treatment due to symptoms of disease and to ensure adequate monitoring. The daily infusions should be given on an inpatient basis at the beginning of induction therapy, followed, when the acute symptoms of APL have resolved and the patient's condition is stable, by outpatient administration for the remaining induction and consolidation treatment period.

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DRUG REGIMEN / CYCLE FREQUENCY

INDUCTION (1 Cycle)

Day / Week	Treatment
Day 1 ***up to*** **Day 60**	**Tretinoin (ATRA)** 45mg/m²/day PO in 2 equally divided doses rounded to the nearest 10mg. Continue until CR or for a maximum of 60 days.
Week 1 **Days 1-5**	**ARSENIC TRIOXIDE** 0.3mg/kg in 100mL 0.9% Sodium Chloride IVI over 2 hours once daily
Weeks 2–8 **2 x / week**	**ARSENIC TRIOXIDE** 0.25mg/kg in 100mL 0.9% Sodium Chloride IVI over 2 hours. Usually on Monday and Thursday.

CONSOLIDATION CYCLES 1-3 (each cycle is 8 weeks)

Proceed to consolidation after induction completed.

Week	Tretinoin (ATRA)
1, 2, 5, 6	45mg/m²/day PO in 2 equally divided doses rounded to the nearest 10 mg
3, 4, 7, 8	No treatment
Week	**ARSENIC TRIOXIDE**
1	0.3mg/kg in 100mL 0.9% Sodium Chloride IVI over 2 hours once daily x 5 days
2, 3, 4	0.25mg/kg in 100mL 0.9% Sodium Chloride IVI over 2 hours 2 x / week
5, 6, 7, 8	No treatment

CONSOLIDATION CYCLE 4 (4 week cycle)

Week	Tretinoin (ATRA)
1, 2	45mg/m²/day PO in 2 equally divided doses rounded to the nearest 10 mg
Week	**ARSENIC TRIOXIDE**
1	0.3mg/kg in 100mL 0.9% Sodium Chloride IVI over 2 hours once daily x 5 days
2, 3, 4	0.25mg/kg in 100mL 0.9% Sodium Chloride IVI over 2 hours 2 x / week

NB. Arsenic Trioxide infusion duration may be extended up to 4 hours if vasomotor reactions, e.g. flushing, tachycardia and dizziness, are observed. If patients suffer severe symptoms or hypotension then the infusion should be stopped until recovery and then recommenced at a reduced rate.

INTRATHECAL PROPHYLAXIS

In the event of an intracranial bleed, consider intrathecal prophylaxis. Discuss at MDT.

RESTAGING

A bone marrow aspirate should be taken at Day 30 to assess initial response to therapy. Thereafter a biopsy should be taken after each cycle of consolidation therapy with particular attention on the RT-PCR analysis of PML-RARA.

If patient is in complete molecular remission, molecular monitoring can be discontinued.

CONTRAINDICATIONS

Pregnancy, breastfeeding, hypersensitivity to the active substance, excipients, other retinoids (for ATRA), and parabens (gelatine capsule preservatives).

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DOSE MODIFICATIONS

Tretinoin (ATRA)	
During induction, ATRA may be temporarily discontinued in the presence of one of the following complications: Differentiation syndrome, Pseudotumour cerebri, Hepatotoxicity.	
Renal impairment	**Hepatic impairment**
GFR < 50mL/min: Reduce dose to 25mg/m^2 daily, in 2 divided doses	Clinical decision due to lack of information. 25mg/m^2 daily, in 2 divided doses is advised by the product license. See Hepatotoxicity section.

ARSENIC TRIOXIDE	
During Induction, Arsenic Trioxide may be temporarily discontinued in the presence of Differentiation syndrome, QT prolongation on ECG or Hepatotoxicity; the drug will need to be discontinued permanently in the event of cardiac arrhythmias or severe neurological toxicity. **Toxicity of Grade 3 or greater** Interrupt / stop treatment - resume only after resolution of toxicity or after recovery to baseline status of the abnormality that prompted the interruption. Resume at 50% of the preceding daily dose. If the toxicity does not recur within 7 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Stop treatment if recurrence of toxicity occurs.	
Renal impairment	**Hepatic impairment**
GFR ≥ 30mL/min: 100% dose GFR < 30ml/min: Consider 50% dose	Mild/moderate impairment (Child-Pugh Stage A or B): 100% dose. Use with caution due to risk of hepatotoxicity Severe impairment (Child-Pugh Stage C): Consider 50% dose

Hepatotoxicity
An increase in bilirubin, AST/ALT, or ALP > 5 X ULN. Temporarily withhold ATRA. If hepatotoxicity persists, temporarily discontinue Arsenic Trioxide.

Resuming Treatment
When symptoms and clinical condition improve, resume ATRA at 50% previous dose during the first 4 days after the disappearance of retinoic acid syndrome, amelioration of pseudotumour cerebri or when bilirubin, AST/ALT or ALP are reduced to < 4 x ULN. In absence of worsening of the previous toxicity, ATRA can be resumed at full dosage. If arsenic trioxide has been stopped due to hepatotoxicity, this can be resumed at 50% of the previous dose for 7 days, when bilirubin, AST/ALT or ALP are reduced to < 4 x ULN. In absence of worsening of the previous toxicity, arsenic trioxide can be resumed at full dosage. In case of reappearance of signs and symptoms of ATRA or arsenic trioxide toxicity, discontinue drug indefinitely during induction therapy.

SPECIAL WARNINGS / PRECAUTIONS / MONITORING

Tretinoin (ATRA)

Pregnancy Warning - Category D
There is a high risk that a severely deformed infant will result if ATRA is administered during pregnancy. Effective contraception must be used by all females during ATRA therapy and for 1 month following discontinuation of therapy. Contraception must be used even when there is a history of infertility or menopause, unless a hysterectomy has been performed.

Leukocytosis at Presentation and Rapidly Evolving Leukocytosis
During ATRA about 40% patients develop rapidly evolving leukocytosis, which is associated with a higher risk of life-threatening complications. WBC > $5x10^9$/L at diagnosis increases risk of a further rapid increase in WBC.

If RA-APL presents with leukocytosis, treatment with high-dose steroids should be initiated immediately. Adding chemotherapy to ATRA if WBC > $5x10^9$/L or if rapid increase in WBC occurs when leukopenic at start of treatment, may lower incidence of RA-APL.

Consider adding cytoreductive chemotherapy to ATRA on:

Day	If **WBC Count**	and **Baseline WBC Count**
1 or 2	> 5 ×10^9/L	n/a
5	≥ 6 ×10^9/L	< 5 × 10^9/L
10	≥ 10 ×10^9/L	< 5 × 10^9/L
28	≥ 15 ×10^9/L	< 5 × 10^9/L

For cytoreduction, Hydroxycarbamide 2g once a day is usually sufficient. Idarubicin doses as per the AIDA protocol can also be used.

Differentiation Syndrome

The syndrome generally occurs during the first month of treatment, in some cases following the first dose of ATRA.

Defined by unexplained fever, weight gain, dyspnoea, acute respiratory distress, radiographic interstitial pulmonary infiltrates, pleural or pericardial effusions, oedema, hepatic, renal, and multi-organ failure, also occasionally accompanied by impaired myocardial contractility and episodic hypotension. The syndrome can present with or without hyperleukocytosis. No single sign or symptom may be considered diagnostic of the syndrome. However, at the earliest manifestations of suspected Differentiation Syndrome (e.g. unexplained respiratory distress), and prior to development of a fulminant syndrome, the following should be immediately undertaken:

- temporarily discontinue ATRA and Arsenic Trioxide
- promptly initiate **Dexamethasone** 10mg IV 12 hourly until resolution of symptoms and signs, for 3 days minimum
- Furosemide when clinically required.

Hyperleukocytosis (WBC >10 x 10^9/L) associated with induction of differentiation may occur in a proportion of patients. This does not require any change in therapy, beyond careful vigilance for development of differentiation syndrome.

Pseudotumour Cerebri
The presence of severe headaches with nausea, vomiting, and visual disorders, generally developing in patients aged < 20 years. It is often necessary to discontinue ATRA temporarily and to administer opiates.

Lipids
Up to 60% experience reversible hypercholesterolemia and/or hypertriglyceridemia. Venous thrombosis and myocardial infarction have been reported in patients ordinarily at low risk for such complications.

Thrombosis risk
Both venous and arterial may involve any organ system, during the first month of treatment.

ARSENIC TRIOXIDE

Electrocardiogram (ECG) Abnormalities

Arsenic Trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia. Previous treatment with anthracyclines may increase the risk of QT prolongation. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging medicinal products, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, Amphotericin B or other conditions resulting in hypokalemia or hypomagnesaemia.

ECG and Electrolyte Monitoring Recommendations

Prior to initiating therapy:

- perform a 12-lead ECG
- for QTc > 500 msec, corrective measures must be completed and the QTc reassessed with serial ECGs prior to considering Arsenic Trioxide
- serum electrolytes (K, Ca, Mg) and Cr must be assessed
- correct all electrolyte abnormalities
- if possible, medicinal products known to prolong QT interval must be discontinued

During therapy:

- Patients with risk factors of QTc prolongation or of torsade de pointes should be monitored with continuous cardiac monitoring (ECG).
- keep Potassium concentrations > 4mmol/L
- keep Magnesium concentrations > 0.75mmol/L
- Patients who reach an absolute QT interval value > 500 msec must be reassessed and immediate action must be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending therapy must be considered.
- If syncope, rapid or irregular heartbeat develops, the patient must be hospitalised and monitored continuously, serum electrolytes assessed, and Arsenic Trioxide therapy temporarily discontinued until the QTc interval regresses to < 460 msec, electrolyte abnormalities corrected, and the syncope and irregular heartbeat ceases.
- obtain ECGs twice weekly, and more frequently for clinically unstable patients, during Induction and Consolidation.

Hyperleukocytosis

In prior cases, the WBC count declined or had normalized by the time of bone marrow remission, and chemotherapy or leukopheresis was not required.

Coagulopathy
A major cause of treatment failure is induction death as a result of haemorrhage, which reflects to varying degree DIC excessive fibrinolysis and proteolysis. Patients with higher presenting WBC > 10 × 10^9/L are at highest risk of haemorrhagic death. Patients with very high presenting leucocyte counts should not undergo leukapheresis, which may precipitate fatal exacerbation of the coagulopathy. High rates of induction death have also been observed when low-dose chemotherapy was used to attempt to reduce WBC in the first instance. Evidence to date suggests that patients with high presenting WBC are best commenced on ATRA and anthracycline based induction therapy. Haemorrhagic deaths may be reduced by rigorous monitoring of the coagulation profile and administration of appropriate replacement therapy until morphological CR has been attained. APTT, prothrombin time, thrombin time, fibrinogen level and platelet count should be checked at least twice daily during the early stages of treatment. Coagulation times should be kept within the normal range using FFP as replacement. Fibrinogen levels may be low due to DIC and cryoprecipitate should be given as replacement aiming for a level of approximately 2g/L. Elevated levels of fibrinogen should be avoided because of the increased risk of thrombosis associated with APL, which may be further exacerbated by ATRA. The platelet count should ideally be maintained > 50 × 10^9/L until morphological remission has been confirmed. Routine use of heparin or anti-fibrinolytic agents is not recommended. Anti-fibrinolytic agents combined with ATRA could potentially increase the inherent risk of thrombotic complications. Nevertheless, anti-fibrinolytic agents could be contemplated in situations of life-threatening haemorrhage in the presence of normal coagulation assays. Recombinant activated Factor VII has also been used in the context of potentially fatal haemorrhage.

INVESTIGATIONS

- Electrolyte, glycaemia levels, haematologic, hepatic, renal and coagulation parameter tests must be monitored at least twice weekly, and more frequently for clinically unstable patients during the Induction phase and at least weekly during the consolidation phase.
- ECG twice weekly (more frequently if clinically unstable)
- Pregnancy Test monthly during treatment (if applicable)

CONCURRENT MEDICATION

Drug	Dose and duration
Allopurinol	300 mg daily for first 14 days of initial induction chemotherapy, starting 24-48 hours before chemotherapy. For high risk patients, follow local tumour lysis prophylaxis protocol.
Aciclovir	200 mg three times a day while neutrophils are < 1 x 10^9/L
Proton pump inhibitor	As per local formulary, while platelets are < 50 x 10^9/L or as clinically indicated

Note: the use of arsenic and ATRA is not very immunosuppressive. Patients do not need to receive antifungal prophylaxis unless there are other clinical factors that indicate the patient is high risk. There is an interaction with azoles and amphotericin B with this regimen so ensure the benefits for antifungal therapy outweigh the risks.

EMETIC RISK

Low - Moderate

INTERACTIONS

Tretinoin (ATRA)
Drugs Metabolised By the Hepatic P450 System ATRA is metabolised by cytochrome P450 system, so there is a potential for interaction with strong CYP3A4 inducers (e.g. rifampicin) or inhibitors (e.g. voriconazole, clarithromycin). Avoid if possible.. **Agents Known to Cause Pseudotumor Cerebri / Intracranial Hypertension** Concomitant administration of agents known to cause pseudotumor cerebri / intracranial hypertension e.g. **Tetracyclines** may increase risk **Vitamin A/other retinoids** ATRA must not be administered concomitantly with vitamin A as hypervitaminosis A could be aggravated. **Anti-fibrinolytic Agents** Cases of fatal thrombotic complications have been reported rarely with concomitant anti-fibrinolytic agents eg. Tranexamic Acid, Aprotinin Microdosed progesterone preparations may be an inadequate method of contraception during ATRA treatment.

ARSENIC TRIOXIDE
Torsade de pointes risk is related to concomitant QT prolonging medicinal products such as: ● class Ia and III antiarrythmics e.g. Quinidine, Amiodarone, Sotalol, Dofetilide ● antipsychotics e.g. Thioridazine ● antidepressants e.g. Amitriptyline ● some macrolides e.g. Erythromycin ● some antihistamines e.g. Terfenadine and Astemizole ● some quinolone antibiotics ● other individual drugs known to increase QT interval e.g. Cisapride ● administration of potassium-wasting diuretics, Amphotericin B or other conditions that result in hypokalemia or hypomagnesaemia

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Tretinoin (ATRA)
Very commonly reported: Headache, fever, weakness, malaise, shivering, haemorrhage, infections, peripheral oedema, pain, chest discomfort, oedema, weight increase, weight decrease, reversible hypercholesterolemia and/or hypertriglyceridemia, rapidly evolving leukocytosis, disseminated intravascular coagulation, elevated LFTs, skin/mucous membrane dryness, rash, pruritus, increased sweating, alopecia, skin changes, bone pain, nausea/vomiting, GI haemorrhage, abdominal pain, mucositis, diarrhoea, constipation, dyspepsia, anorexia, abdominal distention, visual disturbances, ocular disorders, upper respiratory tract disorders, dyspnea, respiratory insufficiency, pleural effusion, pneumonia, rales, expiratory wheezing, otic side effects, arrhythmias, flushing, hypotension, hypertension, phlebitis, dizziness, paresthesias, anxiety, insomnia, depression, confusion, renal insufficiency.
ARSENIC TRIOXIDE
Hyperglycaemia, hypokalaemia, hypomagnesaemia, paraesthesia, dizziness, headache, tachycardia, differentiation syndrome, dyspnoea, diarrhoea, vomiting, nausea, pruritus, rash, myalgia, pyrexia, pain, fatigue, oedema, ALT increase, AST increase, electrocardiogram QT prolongation.

EXTRAVASATION RISK

Arsenic Trioxide: neutral

TREATMENT RELATED MORTALITY

Less than 1%.
In those who develop DS the mortality is approximately 1-5%.
The mortality of underlying disease is higher.

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Julia Wong, Prof Vyas, Cheuk-kie Cheung	New protocol	March 2017	1.0	
Cheuk-kie Cheung	General formatting	May 2017	1.1	
Faouzi Djebbari (Haematology Pharmacist)	Arsenic diluent volume updated. References list updated	Sep 2018	1.2	
Cheuk-kie Cheung	Clarification of dosing schedule, update of NHSE funding and reference.	Nov 2018	1.3	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting. Formatting.	Oct 2019	1.4	Oct 2021
Yen Lim Haematology Pharmacist Andy Peniket, Consultant Haematologist NSSG Myeloid Group	Annual protocol meeting. Updated dosing information for clarification. Updated renal/hepatic dosing, concomitant medications, and drug-specific information.	Nov 2021	2.0	Nov 2023