Tretinoin (ATRA) with Arsenic Trioxide (ATO) Induction Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of patients with newly diagnosed low to intermediate risk Acute Promyelocytic Leukaemia (APL)	C92	00356a	Hospital

**If the reimbursement status is not defined[i], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The treatment is administered until haematological complete remission (CR) or for a maximum of 60 days. Patients who achieve haematological CR progress to Consolidation Therapy with all trans retinoic acid (ATRA) and Arsenic Trioxide (Reference NCCP Regimen 00357).

CR is defined as where the bone marrow is regenerating normal haematopoietic cells and contains <5% blast cells by morphology in an aspirate sample with at least 200 nucleated cells.

Day	Drug	Dose	Route		Cycle
1 until complete remission	Tretinoin (ATRA)	45mg/m^2 in divided doses	[a]PO	n/a	Continuous until Complete Remission (CR) is achieved or up to a maximum of 60 days
1-5 inclusive	Arsenic trioxide	0.3mg/kg	IV infusion	250ml of 0.9% NaCl over 2 hours[b]	Week 1 only
Twice weekly	Arsenic trioxide	0.25mg/kg	IV infusion	250ml of 0.9% NaCl over 2 hours[b]	Week 2 to 8
1 until end of induction	Prednisolone	0.5mg/kg/day	PO		

[a] Tretinoin (ATRA) is available as 10mg capsules. Round dose to nearest 10mg.
The capsules should be swallowed whole with water. They should not be chewed.
It is recommended to take the capsules with a meal or shortly thereafter.

[b] The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required

ELIGIBILTY:

- ECOG status 0-2
- Clinical diagnosis of APL and subsequently confirmed to have PML-RARA rearrangements by a validated test method
- ECOG status 0-2
- Serum total bilirubin ≤3mg/dL (≤51 micromol/L)
- Serum creatinine ≤ 3mg/dL(≤260 micromol/L)

EXCLUSIONS:

- Hypersensitivity to tretinoin (ATRA), retinoids, soya, peanut, arsenic trioxide or any of the excipients
- Significant arrhythmias, ECG abnormalities or neuropathy
- LVEF < 50%
- Breast feeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile, uric acid
- Coagulation profile (Activated Partial Thromboplastin time (APTT), Prothrombin time (PT), fibrinogen level)
- Triglyceride and cholesterol profile
- Pregnancy Test
- ECG
  - For QTc > 450 msec, corrective measures must be completed and the QTc reassessed with serial ECGs prior to considering using arsenic trioxide (see below)
- MUGA or ECHO as clinically indicated

Regular tests:

- FBC, renal and liver profile, uric acid, glucose daily or as clinically indicated
- Coagulation profile: APTT, PT, fibrinogen level at least twice weekly or more frequently as clinically indicated
- Triglyceride and cholesterol profile periodically as clinically indicated
- ECG daily prior to treatment with arsenic trioxide ensuring QTc <450msec (male) / <460msec (female). (QTc to be calculated using validated formula such as Framingham).
- Potassium concentration should be maintained > 4mmol/L
- Magnesium concentration should be maintained > 1.8mg/dL
- Pregnancy test

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- During induction treatment, tretinoin (ATRA) may be temporarily discontinued in the presence of one of the following complications (See Table 1):
    - Differentiation syndrome
    - Pseudotumour cerebri
    - Hepatotoxicity
- Arsenic Trioxide may be temporarily discontinued in the presence of
    - Differentiation syndrome (Table 1)
    - Hepatotoxicity (Table 1)
    - QT prolongation on ECG (see Arsenic Trioxide and QT prolongation below)
- Arsenic Trioxide will need to be discontinued permanently in the event of cardiac arrhythmias or severe neurological toxicity.
- **Arsenic trioxide and Grade ≥3 Adverse reactions**
    - 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.

Table 1: Management of tretinoin (ATRA) and arsenic trioxide related adverse reactions

Adverse Reaction	Action	On recovery
Differentiation Syndrome This is defined by the presence of: unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusion, with or without hyperleucocytosis. No single sign or symptom itself 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 measures opposite should be immediately undertaken: In patients treated with treatinoin (ATRA)and ATO, induction of hyperleucocytosis (WBC >10x10^9/L) associated with induction of blast differentiation on blood film will occur in a proportion of patients. This does not require any change in therapy, beyond careful vigilance for development of differentiation syndrome.	1. Discontinue tretinoin (ATRA) and or arsenic trioxide temporarily. 2. Initiate dexamethasone 10 mg i.v. 12-hourly until disappearance of symptoms and signs, and for a minimum of 3 days. 3. Furosemide when clinically required	Once symptoms/signs improve treatment with tretinoin (ATRA) and or Arsenic trioxide is resumed at 50% of the usual dose for the first 7 days after the disappearance of differentiation syndrome, amelioration of pseudotumour cerebri or when liver tests are reduced to <4 x ULN. Thereafter, in the absence of worsening toxicity, resume 100% dose. In the case of the reappearance of symptoms arsenic trioxide should be reduced to the previous dosage.
Pseudotumour Cerebri (ATRA only) 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 discontinue tretinoin (ATRA) treatment temporarily and to administer opiates.	
Hepatoxicity Bilirubin, AST/ALT or alkaline phosphatase >5 x ULN*	This requires temporary discontinuation of tretinoin (ATRA). If hepatotoxicity persists following discontinuation of tretinoin (ATRA), arsenic trioxide should be temporarily discontinued	

*ULN= Upper Limit of Normal

Arsenic trioxide and QT Prolongation

- ECG and electrolyte levels should be closely monitored during treatment with arsenic trioxide.
- Magnesium concentrations should be maintained above 0.8 mmol/L (1.8mg/dl) and potassium levels above 4 mmol/L (4mEq) taking into consideration possible concomitant treatments that deplete electrolyte levels.
- Framingham formula should be used to adjust the QT interval for heart rate

QTc = QT + 0.154*(1000-RR)

- For increased accuracy the QT interval should be measured on serial ECGs and several successive beats and averaged for each ECG.
- The averaged QT value obtained should be used in the above formula in which all measurements must be expressed in msec.
- Applying this formula a QTc interval > 450msec for men and > 460 msec for women must be considered prolonged.

- Where QTc interval is prolonged arsenic trioxide should be discontinued together with any medication known to prolong the QTc interval and electrolytes should be repleted. The time between discontinuing arsenic trioxide and normalization of the QTc interval may be several days.
- Once QTc is normalized, resume arsenic trioxide at 0.15mg/kg or 0.125mg/kg (50%) for the first 7 days, and then if no further prolongation occurs, resume at 0.19mg/kg for a second week. Thereafter, if no prolongation occurs, resume arsenic trioxide at full dose
- Electrocardiograms must be obtained twice weekly, and more frequently for clinically unstable patients, during induction and consolidation.

Renal and Hepatic Impairment:

Table 2: Dose modifications based on renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Tretinoin (ATRA)	Consideration could be given to dose reduction in renal impairment at the discretion of prescribing consultant	Consideration could be given to dose reduction in hepatic impairment at the discretion of prescribing consultant
Arsenic Trioxide	Caution advised.	Caution advised.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Arsenic trioxide: Moderate (**Refer to local policy).**
Tretinoin: Minimal to low (**Refer to local policy).**
Avoid the use of domperidone due to potential for QT prolongation

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Consider PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Potassium and magnesium supplementation as required.
- Concomitant therapies in case of leucocytosis. Hydroxyurea should be administered to patients who develop leucocytosis after initiation of therapy as detailed in Table 3.

Table 3: Recommendation for initiation of hydroxyurea

WBC (X 10^9/L)	Dose of hydroxyurea
10-50	500mg four times a day
>50	1000mg four times a day
Hydroxyurea should be continued at a given dose to keep the white blood cell count ≤ 10 x 10^9 /L and subsequently tapered	

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Tretinoin:

- **Teratogenecity:** Both tretinoin (ATRA) and arsenic trioxide are teratogenic: Women of child bearing potential must be fully informed of the hazards of becoming pregnant before initiating treatment. They must use reliable contraception without interruption during therapy and for one month after discontinuation of treatment with tretinoin.
- **ECG Abnormalities:** Arsenic trioxide can cause QTc interval prolongation and complete atrioventricular block. Prior to commencement, perform baseline ECG, correct pre-existing electrolyte abnormalities, and if possible cease drugs that may prolong the QTc interval. QTc to be calculated using validated formula such as Framingham. Patients with risk factors of QTc prolongation or risk factors of torsade de pointes should be monitored with continuous cardiac monitoring (ECG). See Arsenic trioxide and QT prolongation under Dose modifications.

DRUG INTERACTIONS:

- Systemic treatment with retinoids may cause elevation of the intracranial pressure. As tetracyclines may also cause elevation of the intracranial pressure, patients must not be treated with tretinoin and tetracyclines at the same time.
- As with other retinoids, tretinoin (ATRA) must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated.
- The effect of food on the bioavailability of tretinoin(ATRA) has not been characterised. Since the bioavailability of retinoids, as a class, is known to increase in the presence of food, it is recommended that tretinoin be administered with a meal or shortly thereafter.
- As tretinoin (ATRA) is metabolised by the hepatic P450 system, there is the potential for alteration of pharmacokinetics parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital and pentobarbital.
- No formal assessments of pharmacokinetic interactions between arsenic trioxide and other therapeutic medicinal products have been conducted.
- QT/QTc prolongation is expected during treatment with arsenic trioxide, and torsade de pointes and complete heart block have been reported. Patients who are receiving, or who have received, medicinal products known to cause hypokalemia or hypomagnesaemia, such as diuretics or amphotericin B, may be at higher risk for torsade de pointes. Caution is advised when arsenic trioxide is coadministered with other medicinal products known to cause QT/QTc interval prolongation or medicinal products known to cause hypokalemia or hypomagnesaemia.
- This list is not exhaustive, current drug interaction databases should be consulted for more information.

ATC CODE:

Tretinoin (ATRA) - L01XX14
Arsenic trioxide - L01XX127

REFERENCES:

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3. AML 17 Version 8.0 (October 2012) 4642-4649.
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6. Vesanoid® Summary of Product Characteristics Accessed May 2018. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1868-001-001_19052015163038.pdf
7. Trisenox® Summary of Product Characteristics Accessed May 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000388/WC500042844.pdf
8. NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting V1 2018.

Version	Date	Amendment	Approved By
1	09/07/2018		Dr Ruth Clifford
2	17/12/2018	Updated dose modification recommendations for arsenic trioxide for management of QTc prolongation	Myeloid CAG
3	10/5/2019	Updated emetogenic potential	Myeloid CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/