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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with low to intermediate risk Acute Promyelocytic Leukaemia (APL) with haematological complete remission (CR) after induction treatment with tretinoin (ATRA) and arsenic trioxide (Ref NCCP Regimen 00356 Tretinoin (ATRA) with Arsenic Trioxide (ATO) Induction Therapy)	C92	00357a	Hospital

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.

Consolidation therapy begins once Complete Remission (CR) has been confirmed on bone marrow and ANC ≥ 1.0 x 10^9/L and platelets > 100 x 10^9/L.
CR is defined as where 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.

Treatment is administered for a total of 7 cycles (1 cycle = 28 days).

- Tretinoin (ATRA) is administered for two weeks followed by two weeks off as shown in Table 1 below for a total of 7 cycles (last cycle administered on week 25-26).
- Arsenic trioxide is administered on Day 1-5 on week 1, twice weekly on week 2-4 (Cycle 1) followed by a 4 week break (Cycle 2). This is repeated up to cycle 7 (last cycle administered on week 25-28).

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment table for Tretinoin (ATRA)-Arsenic trioxide consolidation therapy (see also schedule below)

CYCLE 1,3,5,7					CYCLE 2,4,6			
Drug	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
Tretinoin (ATRA)	Day 1-7 45mg/m^2 in divided doses	Day 1-7 45mg/m^2 in divided doses	**NONE**	**NONE**	Day 1-7 45mg/m^2 in divided doses	Day 1-7 45mg/m^2 in divided doses	**NONE**	**NONE**
Arsenic Trioxide	Day 1-5 0.3mg/kg	Twice weekly 0.25mg/kg			**NONE**			

Administration Details:

Table 2: Administration details for tretinoin (ATRA) and arsenic trioxide

Drug	Route	Diluent and Rate
Tretinoin (ATRA)	PO[a]	
Arsenic trioxide	IV infusion	250ml of 0.9% NaCl over 2 hours[b]
[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.		

Table 3: Treatment Planning Schedule

Week	Tretinoin (ATRA)	Arsenic trioxide
1	Day 1-7, 45mg/m^2 in divided doses	Day 1-5, 0.3mg/kg
2	Day 1-7, 45mg/m^2 in divided doses	Twice weekly 0.25mg/kg
3	None	Twice weekly 0.25mg/kg
4	None	Twice weekly 0.25mg/kg
5	Day 1-7, 45mg/m^2 in divided doses	None
6	Day 1-7, 45mg/m^2 in divided doses	None
7	None	None
8	None	None
9	Day 1-7, 45mg/m^2 in divided doses	Day 1-5, 0.3mg/kg
10	Day 1-7, 45mg/m^{2}in divided doses	Twice weekly 0.25mg/kg
11	None	Twice weekly 0.25mg/kg
12	None	Twice weekly 0.25mg/kg
13	Day 1-7, 45mg/m^2 in divided doses	None
14	Day 1-7, 45mg/m^2 in divided doses	None
15	None	None
16	None	None
17	Day 1-7, 45mg/m^2 in divided doses	Day 1-5, 0.3mg/kg
18	Day 1-7, 45mg/m^2 in divided doses	Twice weekly 0.25mg/kg
19	None	Twice weekly 0.25mg/kg
20	None	Twice weekly 0.25mg/kg
21	Day 1-7, 45mg/m^2 in divided doses	None
22	Day 1-7, 45mg/m^2 in divided doses	None
23	None	None
24	None	None
25	Day 1-7, 45mg/m^2 in divided doses	Day 1-5, 0.3mg/kg
26	Day 1-7, 45mg/m^2 in divided doses	Twice weekly 0.25mg/kg
27	None	Twice weekly 0.25mg/kg
28	None	Twice weekly 0.25mg/kg

ELIGIBILITY:

- ECOG status 0-2
- Clinical diagnosis of APL and subsequently confirmed to have PML-RARA rearrangements by a validated test method
- Serum total bilirubin ≤ 51 micromol/L
- Serum creatinine ≤ 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, glucose
- Coagulation profile (Activated Partial Thromboplastin time (APTT), Prothrombin time (PT), fibrinogen level)
- Triglyceride and cholesterol profile
- Pregnancy test
- ECG
  - For QTc > 460 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
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV

*See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

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 > 0.8mmol/L
- 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 consolidation treatment, tretinoin (ATRA) may be temporarily discontinued in the presence of one of the following complications (See Table 4):
    - Differentiation syndrome (also known as retinoic acid syndrome)
    - Pseudotumour cerebri
    - Hepatotoxicity
- Arsenic Trioxide may be temporarily discontinued in the presence of:
    - Differentiation syndrome (Table 4)
    - Hepatotoxicity (Table 4)
    - 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 4: Management of tretinoin (ATRA) and arsenic trioxide related adverse reactions

Adverse Reaction	Action	On recovery
Differentiation Syndrome (also known as retinoic acid 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.	1. Discontinue tretinoin (ATRA) and / or arsenic trioxide temporarily. 2. Initiate dexAMETHasone 10 mg IV 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.	
Hepatotoxicity 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 and potassium levels above 4 mmol/L, 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 > 450 msec 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 normalisation of the QTc interval may be several days.
- Once QTc is normalised, 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 5: 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	CrCl ≥ 30 ml/min: no need for dose adjustment is expected. CrCl < 30 ml/min: consider 50% of the original dose. Haemodialysis: consider 10 mg three times weekly post-dialysis.	Child-Pugh A and B: no need for dose adjustment is needed. Use with caution due to risk of hepatotoxicity. Child-Pugh C: consider 50% of the original dose.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Arsenic trioxide: Moderate **(Refer to local policy).**

- **Additional caution should be considered when used in combination with medication that has the potential for QT prolongation, please refer to the NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting available here or Refer to local policy.**
  - **Avoid the use of domperidone due to potential for QT prolongation.**

Tretinoin: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: None usually required.

OTHER SUPPORTIVE CARE:

- Anti-viral 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 6.

Table 6: 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.

- **Teratogenicity:** 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 and six months following treatment with arsenic trioxide. Men should use effective contraceptive measures and be advised to not father a child while receiving arsenic trioxide and for 3 months following completion of treatment.
- **Breastfeeding:** Arsenic trioxide is excreted in human milk. Because of the potential for serious adverse reactions in breastfeeding infants and children from arsenic trioxide, breastfeeding must be discontinued prior to and throughout administration, and for two weeks after the last dose. Breast-feeding must be discontinued prior to initiation of therapy with tretinoin.
- **ECG Abnormalities:** Arsenic trioxide can cause QTc interval prolongation and complete atrioventricular block. QTc prolongations have been observed in connection with combination therapy of tretinoin and arsenic trioxide. 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.
- **Hyperleukocytosis:** Combination therapy of tretinoin with arsenic trioxide has been associated with the development of hyperleukocytosis. Hydroxyurea should be administered to patients to keep the white blood cell count ≤ 10 x 10^9/L (see Table 6).
- **Differentiation syndrome (also known as retinoic acid 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 – it can be fatal. See Table 4 for management.
- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.

Tretinoin (ATRA):

- **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. See Table 4 for management.

DRUG INTERACTIONS:

- Systemic treatment with retinoids may cause elevation of intracranial pressure. As tetracyclines may also cause elevation of intracranial pressure, patients must not be treated with tretinoin (ATRA) 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 (ATRA) 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. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil and diltiazem.
- 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 hypokalaemia 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 hypokalaemia or hypomagnesaemia.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	09/07/2018		Dr Ruth Clifford
2	17/12/2018		Myeloid CAG
3	10/05/2019	Updated emetogenic potential	Myeloid CAG
4	20/09/2023	Updated tests (baseline), dose modifications in renal / hepatic impairment, emetogenic potential, other supportive care, adverse effects and drug interactions. Amended Table 4 (differentiation syndrome). Amended all units to SI units.	Dr Eibhlin Conneally

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.