Indication	Newly diagnosed low to intermediate risk APML and relapsed/refractory APML.
Treatment Intent	Curative
Frequency and number of cycles	Induction: Single cycle Consolidation: Every 8 weeks for 4 cycles NB The arsenic trioxide schedule in the AML-17 trial for newly diagnosed and relapsed/refractory patients and the combination of ATRA and arsenic in relapsed/refractory are both currently unlicensed in the UK. Clinicians must be mindful of their individual responsibilities when prescribing unlicensed doses.
Monitoring parameters pre-treatment	**Pre-treatment Tests – BASELINE:** • **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • CMV, IgG and HIV status. • FBC, clotting screen, U&Es, magnesium, potassium and LFTs • Correct any pre-existing electrolyte abnormalities. • 12-lead ECG assessment to ensure that the QTc interval <460msec • Echo/MUGA if cardiac history, elderly or risk factors for cardiac disease • Medication review: if possible drugs that are known to prolong QT interval should be discontinued **Pre-treatment Tests- During therapy:** • FBC, clotting screen, U&Es, LFTs, glycaemia levels at least twice weekly (and more frequently in clinically unstable patients) during induction and at least weekly during consolidation. • Magnesium and Potassium: Serum potassium must be kept above 4mmol/l and the serum magnesium above 0.74 mmol/L before each dose. • ECG assessment to ensure that the QTc interval <500msec before each dose. **Supportive Care** • Potassium and magnesium supplementation are often required to keep electrolytes within desired limits. **Induction Single cycle:** • Patients should have post cycle 1 (Induction) bone marrow assessment including molecular studies and patients should enter consolidation if they are in complete morphological remission and there is an absolute neutrophil count of more than 1.0 x 10^9/l and platelet count of at least 100 x 10^9/l. **Consolidation: 4 cycles:**

	• Marrow samples will be collected after each consolidation cycle of ATO, to be tested by RQ-PCR for assessment of molecular remission. Patients who do not achieve molecular remission by the end of the 3rd consolidation cycle will be considered as molecular resistant. • **Infusion related reactions:** • The infusion duration of arsenic trioxide may be extended up to 4 hours if vasomotor reactions (e.g. flushing, tachycardia, dizziness) are observed. If severe symptoms or hypotension, the infusion should be stopped until recovery, then restarted at a reduced rate. • **Renal Impairment** o Arsenic Trioxide: The plasma clearance of the active metabolite in patients with creatinine clearance less than 30ml/min was 40% lower when compared with patients with normal renal function, therefore patients with CrCl <30ml/min may require a dose reduction. Clinical decision o Tretinoin: Limited information - Manufacturer advises that the dose be decreased to 25mg/m^2 as a precautionary measure as studies have not been done in patients with renal dysfunction. Clinical decision • **Hepatic impairment** o Arsenic Trioxide: If serum bilirubin, AST/ALT, or alkaline phosphatase >5 times the normal upper level temporarily suspend arsenic o Tretinoin: If serum bilirubin, AST/ALT, or alkaline phosphatase >5 times the normal upper level temporarily suspend tretinoin. When serum bilirubin, AST/ALT or alkaline phosphatase are reduced to <4 times the normal upper level tretinoin may be resumed at 50% dose. If liver enzymes do not worsen, full dose tretinoin may be resumed. If hepatoxicity persists following discontinuation of tretinoin, arsenic should be temporarily discontinued. • **Dose Modifications and Toxicity:** **Cardiac toxicity** • Arsenic trioxide can cause QT prolongation and complete AV block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia. • During therapy with arsenic trioxide, potassium concentrations must be kept above 4mmol/L and magnesium concentrations must be kept above 0.74mmol/L. Patients who reach an absolute QTc interval value >500msec must be reassessed and immediate action must be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending arsenic trioxide therapy must be considered. In view of this, during therapy U&Es should be checked on every day of treatment and the serum potassium must be kept above 4mmol/L and the serum magnesium above 0.74mmol/L • If syncope, rapid or irregular heartbeat develops, the patient must be hospitalised and monitored continuously, serum electrolytes must be assessed, arsenic trioxide therapy must be temporarily discontinued until the

	QTc interval regresses to below 460msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. • **Differentiation Syndrome (Retinoic Acid Syndrome)** • This is reported to occur in up to 25% of patients and should be treated as recommended for the Retinoic acid/ATRA syndrome. • At the earliest manifestation of suspected Differentiation Syndrome (e.g. unexplained respiratory distress), and prior to development of a full-blown syndrome, the following measures should be immediately undertaken: o Temporary discontinuation of arsenic treatment o Prompt initiation of dexamethasone 10mg intravenously 12-hourly until disappearance of symptoms and signs, and for a minimum of 3 days. o Furosemide when clinically required. • For patients at a higher risk of developing "differentiation syndrome" (e.g. presenting with an elevated WCC) consideration should be given to admitting the patient for treatment. • **Hyperleukocytosis** Treatment with arsenic has been associated with the development of hyperleukocytosis (WBC >/=10) in some relapsed/refractory APL patients. Hyperleukocytosis was never treated with additional chemotherapy and resolved on continuation of arsenic. • **Pseudotumour cerebri** can occur with tretinoin presenting as a severe headache, vomiting and visual disorders. It may be necessary to reduce the tretinoin dose and treat with diuretics (acetazolamide), corticosteroids and/or analgesics. • **Other treatment related toxicities** During treatment arsenic must be temporarily interrupted in the event of a grade 3 or greater toxicity possibly related to arsenic. Treatment should be interrupted for: o Nephrotoxicity (serum creatinine >3.5 x ULN) o Significant neurological impairment o Severe peripheral neuropathy • Patients must resume treatment only after resolution of the toxic event or after recovery to baseline. In such cases, treatment must resume at 50% of the preceding daily dose. If the toxic event 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. Patients who experience a recurrence of toxicity must be removed from treatment. • **Pregnancy and contraceptive guidance:** o Tretinoin is highly teratogenic. Women of child bearing potential must have a negative pregnancy test before starting treatment and repeated monthly until 6 months after stopping treatment. Due to the genotoxic risk of arsenic compounds, women of childbearing potential must use effective contraceptive measures during treatment and for 6 months following completion of treatment.

	○ Men should use effective contraceptive measures and be advised to not father a child while receiving treatment, and for 3 months following completion of treatment. • **Interactions** ○ Avoid concomitant use of ATRA and agents known to cause pseudotumor cerebri/intracranial hypertension e.g. tetracyclines may increase risk ○ Avoid concomitant use of arsenic and QT prolonging medicinal products or those that may result in hypokalaemia or hypomagnesaemia. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
Reference(s)	DERBY-BURTON LOCAL CANCER NETWORK DOC NO: HCCPG B86 SPC accessed online 11.07.2022 KMCC protocol HAEM-AML-027 V1

NB For funding information refer to CDF and NICE Drugs Funding List

Induction: Single Cycle

Day/Week	Drug	Dose	Route	Directions
Day 1 until complete remission Or maximum of 60 days	**Tretinoin (ATRA)**	**45mg/m^2/day**	PO	TWO equally divided doses. Round to the nearest 10mg increment.
Week 1: Day1-5	**Arsenic Trioxide (ATO)**	**0.3mg/kg/day for 5 days**	IV	IV infusion in 100ml sodium chloride 0.9% over 1-2 hours
Weeks 2-8 Twice weekly	**Arsenic Trioxide (ATO)**	**0.25mg/kg twice weekly for 7 weeks**	IV	IV infusion in 100ml sodium chloride 0.9% over 1-2 hours
TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 consecutive days
	Chlorhexidine Gluconate	0.2%	TOP	Rinse mouth with 10ml four times a day
	Allopurinol (or Rasburicase)	300mg	PO	Once daily for 28 days Cycle 1 only Clinical Decision: high risk of tumour lysis syndrome

Consolidation: every 8 weeks for 4 cycles

Cycles 1-3

Day/Week	Drug	Dose	Route	Directions
Day 1 -14 and 29-42	**Tretinoin (ATRA)**	**45mg/m^2/day**	PO	TWO equally divided doses. Round to the nearest 10mg increment.
Week 1: day 1 - 5	**Arsenic Trioxide (ATO)**	**0.3mg/kg/day for 5 days**	IV	IV infusion in 100ml sodium chloride 0.9% over 1-2 hours
Weeks 2 - 4: Twice weekly	**Arsenic Trioxide (ATO)**	**0.25mg/kg twice weekly**	IV	IV infusion in 100ml sodium chloride 0.9% over 1-2 hours
Weeks 5 - 8	Arsenic Trioxide (ATO)			No Treatment
TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously
	Chlorhexidine Gluconate	0.2%	TOP	Rinse mouth with 10ml four times a day

Cycle 4 only

Day/Week	Drug	Dose	Route	Directions
Day 1-14 only	**Tretinoin (ATRA)**	**45mg/m^2/day**	PO	TWO equally divided doses. Round to the nearest 10mg increment.
Week 1: day 1 – 5	**Arsenic Trioxide (ATO)**	**0.3mg/kg/day for 5 days**	IV	IV infusion in 100ml sodium chloride 0.9% over 1-2 hours
Weeks 2-4: Twice weekly	**Arsenic Trioxide (ATO)**	**0.25mg/kg twice weekly**	IV	IV infusion in 100ml sodium chloride 0.9% over 1-2 hours
Weeks 5 - 8	Arsenic Trioxide (ATO)			No Treatment
TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously
	Chlorhexidine Gluconate	0.2%	TOP	Rinse mouth with 10ml four times a day

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