Arsenic trioxide

Indication

Induction of remission, and consolidation in acute promyelocytic leukaemia (APML) (characterised by the presence of the t[15;17] translocation or the PML/RAR-alpha gene) in adults with:
- Newly diagnosed untreated, low-to-intermediate risk disease (defined as a white blood cell count ≤ 10 x 10^9/L), when given with all-trans-retinoic acid (tretinoin, ATRA).
- Relapsed or refractory APML (previous treatment should include a retinoid and chemotherapy).

(NICE TA526)

ICD-10 codes

Codes with a prefix C92.4

Regimen details

Newly diagnosed APML if used in conjunction with tretinoin (see separate protocol)

NOTE this dosing schedule is as per the AML 17 clinical trial not the product licence and therefore should be considered unlicensed.

Induction

Day	Drug	Dose	Route
1-5 (week 1) then twice a week for weeks 2-8	Arsenic trioxide	0.30mg/kg daily on days 1-5 of week 1 then 0.25mg/kg twice a week for weeks 2-8	IV infusion

Consolidation

Commence 4 weeks after induction treatment is completed (i.e. 12 weeks from the start of therapy).
Each cycle of consolidation treatment is 8 weeks long with 4 weeks of treatment followed by 4 weeks without treatment.
This should be repeated for a total of 4 cycles.

Day	Drug	Dose	Route
1-5 (week 1) then twice a week for weeks 2-4	Arsenic trioxide	0.30mg/kg daily on days 1-5 of week 1 then 0.25mg/kg twice a week for weeks 2-4	IV infusion

Relapsed or refractory APML, NOT used in conjunction with tretinoin:

Induction

Day	Drug	Dose	Route
1-50*	Arsenic trioxide	0.15mg/kg/day	IV infusion

* Daily until bone marrow remission is achieved. If not achieved by day 50 then dosing should be discontinued.

Consolidation

Commence 3-4 weeks after completion of induction therapy.

Day	Drug	Dose	Route
1-5 each week for 5 weeks*	Arsenic trioxide	0.15mg/kg/day	IV infusion

* total of 25 doses given (5 days per week, followed by 2 days interruption, repeated for 5 weeks in total).

Cycle frequency
As above

Number of cycles
As above

Administration
Arsenic trioxide is administered in 100-250mL sodium chloride 0.9% over 2 hours.

Patients should be monitored regularly during the infusion and good oral fluid intake should be encouraged. If patients suffer vasomotor symptoms including flushing, tachycardia and dizziness the rate of the infusion should be reduced. If patients suffer severe symptoms or hypotension then the infusion should be stopped until recovery and then recommenced at a reduced rate. Headache may be treated with paracetamol.

If symptoms persist, consider paracetamol as premedication for future doses and administer arsenic trioxide over 4 hours.

Pre-medication
None required

Emetogenicity
This regimen has moderate emetogenic potential.

Additional supportive medication
Ciprofloxacin during periods of neutropenia as per local antimicrobial policy.
Antifungal prophylaxis during periods of neutropenia as per local antimicrobial policy.

Extravasation
Arsenic trioxide is an irritant (group 3).

Investigations – pre first cycle

Investigation	Validity period
FBC	12 hours
U+Es* (including creatinine)	24 hours
Magnesium	24 hours
Glucose	24 hours
LFTs	24 hours
APPT and PT /fibrinogen	12 hours
Bone profile	24 hours
ECG (and echocardiogram if clinically indicated)	Baseline

Pregnancy test: mandatory for all women of child bearing age prior to commencing treatment.

*Electrolyte abnormalities must be corrected prior to commencing treatment.

Investigations - during initial induction period – twice weekly

Investigation	Validity period	Action
FBC	12-24 hours	Keep platelets 30-50 x 10^9/L until morphological remission confirmed
APPT/PT	12-24 hours	Keep within the normal range using FFP until morphological remission confirmed
Fibrinogen	12-24 hours	Cryoprecipitate should be given aiming for fibrinogen >2g/L until morphological remission confirmed
U+Es (including creatinine)	24-48 hours	Maintain: Potassium > 4.0mmol/L Magnesium > 0.74mmol/L
Glucose	24-48 hours	
LFTs	24-48 hours	If bilirubin or AST/ALT> 5 x ULN withhold tretinoin if applicable; if abnormalities persist withhold arsenic trioxide
Bone profile	24-48 hours	
ECG	72-96 hours (More frequently if clinically indicated)	If QT interval value > 500 msec re-assess, address other risk factors and consider suspension of arsenic trioxide, if cardiac symptoms discontinue until QTc interval is < 500 msec.

Investigations - during initial consolidation period - weekly

Investigation	Validity period	Action
FBC	7 days	
APPT/PT	7 days	
Fibrinogen	7 days	
Glucose	7 days	
U+Es (including creatinine)	7 days	Maintain: Potassium > 4.0mmol/L - ULN Magnesium > 0.74mmol/L - ULN
Glucose	7 days	
LFTs	7 days	
Bone profile	7 days	
ECG	72-96 hours (More frequently if clinically indicated)	If QT interval value >500 msec re-assess, address other risk factors and consider suspension of arsenic trioxide, if cardiac SE discontinue until QTc interval is less than 460 msec.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Stage of treatment	Investigation	Limit
Initial treatment	FBC	Treatment should commence regardless of FBC
Consolidation courses	FBC	Neutrophils >1.5 x 10^9/L Platelets >100 x 10^9/L
Any	Potassium	> 4.0mmol/L
	Magnesium	> 0.74mmol/L
	CrCl	≥ 30mL/min
	QTc interval on ECG	< 460msec
	Bilirubin	< 5 x ULN
	ALT/AST	< 5 x ULN
	Alkaline Phosphatase	< 5 x ULN

Dose modifications

- **Haematological toxicity**

As above.

- **Renal impairment**

Limited data available. Caution is advised when using arsenic trioxide in patients with renal impairment. The experience in patients with severe renal impairment is insufficient to determine if dose adjustment is required. Consider dose reduction if CrCl < 30mL/min.
The use of arsenic trioxide in patients on dialysis has not been studied.
If renal function deteriorates discuss with consultant.

- **Hepatic impairment/Hepatic toxicity**

Limited data available. Caution is advised when using arsenic trioxide in patients with hepatic impairment. The experience in patients with severe hepatic impairment is insufficient to determine if dose adjustment is required. Consultant decision. If hepatic function deteriorates discuss with consultant.

If bilirubin, AST/ALT, or ALP > 5 X ULN, temporarily withhold treatment. If hepatotoxicity persists, discontinue treatment.

Any toxicity ≥ grade 3: withhold treatment, resume at 50% dose after resolution or recovery to baseline. If toxicity dose not recur after 7 days the dose may be escalated to previous level. Treatment should be discontinued if toxicity recurs.

- **Other toxicities**

During induction, arsenic may be temporarily discontinued in the presence of differentiation syndrome, QT prolongation or hepatotoxicity. Arsenic should be permanently discontinued in the event of cardiac arrhythmias or severe neurological toxicity.

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, which can be fatal.
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 (see interactions), a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, amphotericin B or other conditions that result in hypokalaemia or hypomagnesaemia.
Tachycardia, pericardial effusions and ventricular extrasystoles may also be seen.

Adverse effects - for full details consult product literature/ reference texts

Serious side effects

Prolongation of the QT interval
Atrial fibrillation
Cardiac arrest
Haemorrhage
Tachycardia
Myelosuppression
Respiratory toxicity -dyspnoea, hypoxia, pleural effusion, pleuritic pain and pulmonary alveolar haemorrhage.
Differentiation syndrome
Encephalopathy
Hepatotoxicity

Frequently occurring side effects

Myelosuppression
Peripheral neuropathy
Headache, paraesthesia, dizziness
Nausea, vomiting
Diarrhoea
Pruritus, rash
Infusion related vasomotor symptoms
Hypotension
Abnormal LFTs
Electrolyte disturbances – hypokalaemia, hypomagnesaemia
Hyperglycaemia
Arthralgia
Fatigue

Significant drug interactions – for full details consult product literature/ reference texts

Medications known to cause torsades de points (including amiodarone, clarithromycin, chlorpromazine, chloroquine, domperidone, erythromycin, haloperidol, methadone, pentamidine, sotalol) – increased risk of torsades de points.
Medications known to cause hypokalaemia and/or hypomagnesaemia (diuretics, amphotericin B) – increased risk of torsades de points.
Hepatotoxic medications – use with caution if co-administered.

Additional comments

Differentiation syndrome
Patients should be advised to immediately report fever, sudden weight gain, fluid retention, musculoskeletal pain or dyspnoea. This may be caused by differentiation syndrome.
If this occurs check ABGs, CXR and commence dexamethasone 10mg IV BD for at least 3 days - discuss with consultant**.**

References

- Summary of Product Characteristics Arsenic Trioxide (TEVA) accessed 18 September 2019 via http://www.medicines.org.uk
- National Institute for Health and Clinical Excellence. NICE TA526. Accessed 18 September 2019 via www.nice.org.uk
- AML 17 Clinical Guidelines
- Management of acute promyelocytic leukaemia: recommendations from an expert panel on behalf of the European LeukemiaNet
- Burnett AK et al (2015) Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol. 16(13):1295-1305

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