Tretinoin - ATRA (All Trans Retinoic Acid)

Indication

Treatment of acute promyelocytic leukaemia (APML)

Used in combination with chemotherapy.

ICD-10 codes

C92.4

Regimen details

APML induction therapy used alongside chemotherapy (idarubicin) OR used alongside arsenic trioxide:

Day	Drug	Dose	Route
1-60 maximum (Until haematological CR or maximum 60 days)	Tretinoin	45mg/m^2/day in 2 divided doses (i.e 22.5mg/m^2 BD) (Rounded to nearest 10mg)	PO

THEN

First consolidation used alongside chemotherapy (idarubicin):

Day	Drug	Dose	Route
1-15	Tretinoin	45mg/m^2/day in 2 divided doses (i.e 22.5mg/m^2 BD) (Rounded to nearest 10mg)	PO

Second consolidation cycle used alongside chemotherapy (mitoxantrone):

Day	Drug	Dose	Route
1-15	Tretinoin	45mg/m^2/day in 2 divided doses (i.e 22.5mg/m^2 BD) (Rounded to nearest 10mg)	PO

Third consolidation cycle when used alongside chemotherapy (idarubicin):

Day	Drug	Dose	Route
1-15	Tretinoin	45mg/m^2/day in 2 divided doses (i.e 22.5mg/m^2 BD) (Rounded to nearest 10mg)	PO

OR

APML Consolidation therapy when used alongside arsenic trioxide:

Day	Drug	Dose	Route
1-14	Tretinoin	45mg/m^2/day in 2 divided doses (i.e 22.5mg/m^2 BD) (Rounded to nearest 10mg)	PO

Each cycle is intended to be 4 weeks ie treatment will be administered for 2 weeks on followed by 2 weeks off, for a total of 7 cycles.

Cycle frequency

Each consolidation course should be commenced at haematological recovery from the previous course (neutrophils >1.5 x 10^9/L and platelets >100 x 10^9/L) with at least 2 weeks off between cycles.

Number of cycles
As above

Administration
Tretinoin is available as 10mg capsules. Capsules should be swallowed whole (not chewed) with water. It is recommended that the capsules are taken with or after a meal.

Pre-medication
Nil

Emetogenicity
Not known to be emetogenic.
(However idarubicin is highly emetogenic and mitoxantrone is moderately emetogenic therefore local policy needs to be followed when used in combination with these agents).

Additional supportive medication
Ciprofloxacin as per local antimicrobial policy.
Antifungal prophylaxis as per local antimicrobial policy.
Mouthwashes as per local policy.

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	12 hours
U+Es (including creatinine)	24 hours
LFTs	24 hours
APPT and PT /fibrinogen	12 hours
Bone profile, Cholesterol and triglycerides	7 days
Calcium	7 days

Pregnancy test must be done for all women of child bearing age prior to therapy.
Cardiac assessment if clinically indicated.

Investigations - during initial induction period

Investigation	Validity period	Action
FBC	12 hours	Keep platelets 30-50 x 10^9/L until morphological remission confirmed
APPT/PT	12 hours	Keep within the normal range using FFP until morphological remission confirmed
Fibrinogen	12 hours	Cryoprecipitate should be given aiming for fibrinogen >2g/L until morphological remission confirmed
U+Es (including creatinine)	24 hours	
LFTs	24 hours	
Bone profile	24 hours	
Cholesterol and triglycerides	72 hours	
Calcium	72 hours	

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. If WCC >10 x 10^9/L then idarubicin should be started as soon as possible and within a few days of starting tretinoin
Consolidation courses	FBC	Neutrophils >1.5 X 10^9/L Platelets >100 x 10^9/L

Dose modifications

- **Haematological toxicity**

Each cycle should commence at haematological recovery from the previous cycle. This is defined as neutrophils > 1.5 x 10^9/L and platelets > 100 x 10^9/L.

- **Renal impairment**

There is limited information on use in patients with renal impairment. Consider reducing dose to 25mg/m^2 or withholding tretinoin as a precautionary measure (consultant decision).

- **Hepatic impairment**

There is limited information on use in patients with hepatic impairment. Consider reducing dose to 25mg/m^2 or withholding tretinoin as a precautionary measure (consultant decision).
If hepatoxicity persists following discontinuation of tretinoin and the patient is also receiving arsenic trioxide, this should also be temporarily discontinued.

- **Other toxicities**

Retinoic acid syndrome:
Unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, hypotension, pleural or pericardial effusions and hepatic, renal or multi organ failure. Frequently associated with hyperleucocytosis but may occur at any level of WCC. This is a major cause of mortality in patients treated with ATRA. If suspected discuss with consultant immediately. Administer dexamethasone 10mg IV 12 hourly for a minimum of 3 days and until resolution of symptoms. Discontinue ATRA.

As soon as the patients' symptoms and clinical condition improves, treatment with ATRA should be resumed at 50% of the previous dose during the first 4 days after the disappearance of retinoic acid syndrome. Thereafter, in absence of worsening of the previous toxicity, ATRA should be resumed at full dosage.

In case of reappearance of signs and symptoms of ATRA toxicity, the drug must be discontinued indefinitely during induction therapy.

Psuedotumour cerebri:
May occur in patients under 20 years of age. Presents with headaches, nausea, vomiting and visual disturbances. Discuss with consultant and temporarily discontinue ATRA.

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

- **Serious side effects**

Myelosuppression
Retinoic acid syndrome (see above)
Pseudo tumor cerebri (see above)
Cerebrovascular accident
Myocardial infarction
Respiratory failure

Pancreatitis
Necrotizing fasciitis
Thrombosis, vasculitis

- **Frequently occurring side effects**

Decreased appetite
Confusion, anxiety, depression, insomnia
Dizziness, paraesthaesia
Visual disturbances, conjunctival disorders
Hearing impairment
Arrhythmias
Nausea, vomiting
Diarrhoea, constipation
Erythema, rash, pruritus

- **Other side effects**

Chills, malaise
Flushing
Dry mouth
Alopecia
Hypercalcaemia
Raised cholesterol and triglycerides
Raised transaminases

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

Tetracyclines: both tetracyclines and tretinoin may cause elevation of the intracranial pressure and therefore should not be used concurrently.
Vitamin A: tretinoin must not be administered with vitamin A because symptoms of hypervitaminosis A could be aggravated.

Tretinoin is metabolised by the cytochrome P450 system and so potentially interacts with enzyme inducers (such as rifampicin, glucocorticoids, phenobarbitone) and enzyme inhibitors (ketoconazole, erythromycin, verapamil, diltiazem and ciclosporin).

Antifibrinolytic agents (including tranexamic acid, aprotonin): fatal thrombotic complications have been reported.

Additional comments

See separate guidelines for idarubicin and mitoxantrone.

Tretinoin contains soya-bean oil, and therefore is contraindicated in patients allergic to soya or peanut.

Tretinoin is highly teratogenic. Women of child bearing potential must be fully informed of the hazards of becoming pregnant during and one month after completing treatment. Women of child bearing potential must have a negative pregnancy test before starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping tretinoin. If a woman taking tretinoin thinks she may be pregnant she must stop the drug immediately. Women of child bearing potential must use reliable contraception while on tretinoin and for one month after.

References

- Summary of Product Characteristics Tretinoin (Intrapharm) accessed 17 December 2014 via http://www.medicines.org.uk
- AML 17 Clinical Guidelines
- Management of acute promyelocytic leukaemia: recommendations from an expert panel on behalf of the European LeukemiaNet

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