

## EMERGENCY ATRA (All-Transretinoic Acid/ Tretinoin)

### INDICATION

Induction treatment for suspected or proven Acute Promyelocytic Leukaemia (APL).

### TREATMENT INTENT

Curative. Initial treatment to reduce adverse events from coagulopathy

### PRE-ASSESSMENT

1. Undertake relevant history and examination; especially assessing for bleeding/bruising and infection/infective foci
2. Establish the diagnosis of suspected or proven APL. Ensure histology confirmed prior to administration of chemotherapy and document in notes.
3. Blood tests: FBC, U&Es, LFTs, calcium, LDH, urate, magnesium.
4. **Tests and treatment of APL coagulopathy** – APTT, prothrombin time, thrombin time, fibrinogen level and platelet count should be checked at least twice daily during the early stages of treatment. Coagulation times should be kept within the normal range using FFP replacement. Fibrinogen levels may be low due to DIC and cryoprecipitate should be given as replacement aiming for a level of approximately 2 g/L. Elevated levels of fibrinogen should be avoided because of the increased risk of thrombosis associated with APL, which may be further exacerbated by ATRA. The platelet count should ideally be maintained above  $50 \times 10^9/L$  until morphological remission has been confirmed. Thereafter, check PT, APTT and Fibrinogen daily until morphological remission.
5. BM – MGG and samples for RT-PCR (molecular diagnostics) and cytogenetics
6. **Exclude pregnancy in all women of childbearing potential.** There is a high risk that a severely deformed infant will result if ATRA is administered during pregnancy. Effective contraception must be used by all females during ATRA therapy and for 1 month following discontinuation of therapy.
7. Record performance status (WHO/ECOG).
8. Record weight and height.
9. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines).
10. Consent – ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in notes all information that has been given. Obtain written consent prior to treatment.
11. Prehydration and tumour lysis prevention – see Tumour lysis protocol
12. Patients who present with a WBC  $>10 \times 10^9/L$  have a higher chance of developing differentiation syndrome (DS). Consider prophylactic corticosteroids (e.g. dexamethasone 10mg bd) with patients with WBC  $>10 \times 10^9/L$  and other high risk features e.g. renal failure. Once DS is suspected, stop ATRA, give dexamethasone (10mg bd IV) until symptoms resolve.
13. Treatment should be agreed in the relevant MDT (after commencement of treatment in most cases in emergency/ urgent setting).

## DRUG REGIMEN

<b>Tretinoin (ATRA)</b>	<p>45mg/m<sup>2</sup>/day PO in 2 equally divided doses (in other words give 22.5mg m<sup>2</sup> twice a day), rounded to the nearest 10mg increment (until first CR is achieved or up to 60 days continuous treatment).</p> <p><b>Consider starting as single agent for up to 7 days; once diagnosis of APL is established add in chemotherapy as per current protocol</b></p>
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When the WBC count at the start of therapy is  $> 5 \times 10^9/L$ , consider starting chemotherapy with tretinoin on day one.

When the WBC count at the start of therapy is  $< 5 \times 10^9/L$  but rapidly increases during tretinoin therapy, consider adding chemotherapy to the tretinoin regimen.

Please refer to the ATRA + Arsenic Trioxide or AIDA protocols for more details on this cytoreduction.

All non-APL patients should receive chemotherapy immediately after non-APL diagnosis is established.

If patient is unable to swallow capsules whole, please refer to: [ML 67 - Guidance for administering tretinoin \(ATRA\) capsules in haematology patients with swallowing difficulties and NG/PEG tubes](#)

## CYCLE FREQUENCY

This is a one-off use of the drug for up to 1 week whilst the diagnosis of APL is being firmly established and treatment plan made. ATRA is usually continued during induction treatment until complete remission or up to a maximum of 60 days.

## DOSE MODIFICATIONS

### Haematologic

No dose modifications required for myelosuppression.

### Non-Haematologic

During induction treatment, ATRA may be temporarily discontinued in the presence of one of the following complications: differentiation syndrome (ATRA syndrome), pseudotumour cerebri, hepatotoxicity.

Renal impairment	Hepatic impairment
GFR $\geq 30$ mL/min: 100% dose GFR $< 30$ mL/min: Consider 50% dose	Mild/moderate impairment (Child-Pugh Stage A or B): 100% dose. Use with caution due to risk of hepatotoxicity Severe impairment (Child-Pugh Stage C): Consider 50% dose

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## INVESTIGATIONS

- Pregnancy test at start of treatment for women of childbearing potential and on a monthly basis during therapy
- Full blood count, renal and liver profiles
- Clotting screen (including D-dimers, fibrinogen). PT, APTT and Fibrinogen daily until morphological remission.
- Biochemistry – including U+E, LFTs, Ca<sup>2+</sup>, Phosphate.
- Triglyceride and cholesterol levels.
- Bone marrow assessment for MGG, cytogenetics, molecular assessment of PML-RARA and RARA-PML, microscopic assessment of PML bodies.
- Flow cytometry

## CONCURRENT MEDICATIONS

- Allopurinol 300mg OD for 14 days starting 24-48 hours pre-chemotherapy.
- Patients at high risk of tumour lysis (i.e. presenting with a white count of >10x10<sup>9</sup>/L and/or with bulk disease: refer to tumour lysis protocol).
- **Prophylaxis against retinoic acid / 'ATRA' or 'differentiation' syndrome:** Patients who present with a WBC >10 x10<sup>9</sup>/L should receive Dexamethasone 10 mg IV 12-hourly for the first 5 days of chemotherapy
- **Avoid tranexamic acid whilst on ATRA**

## EMETIC RISK

Low

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

### Differentiation Syndrome (ATRA syndrome/ 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 hyperleukocytosis, hypotension, oedema, hepatic, renal, multi-organ failure. No single sign or symptom itself may be considered diagnostic of the syndrome. However, at the earliest manifestations of suspected ATRA Syndrome (e.g. unexplained respiratory distress), and prior to development of a full blown syndrome, the following measures should be immediately undertaken:

- Temporary discontinuation of ATRA treatment.
- Promptly initiate dexamethasone 10 mg IV 12-hourly until disappearance of symptoms and signs, and for a minimum of 3 days
- Furosemide when clinically required.

**Note:** In patients treated with ATRA, induction of hyperleukocytosis (WBC >10x10<sup>9</sup>/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.

### 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, it is often necessary to temporarily discontinue ATRA treatment and to administer opiates.

### Hepatotoxicity

Bilirubin, AST/ALT, or ALP  $>5 \times$  ULN. This requires a temporary suspension of the ATRA. As soon as the symptoms and the patient's clinical condition improves, treatment with ATRA will be resumed at 50% of the previous dose during the first 4 days after the disappearance of retinoic acid syndrome, amelioration of pseudotumour cerebri or when serum bilirubin, AST/ALT or alkaline phosphates are reduced to  $<4 \times$  ULN. 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. However, patients who enter the maintenance phase of the Spanish schedule should receive ATRA where possible.

### Others

- Headache is common and usually requires analgesia. Bone pain, occasionally requiring analgesic treatment, has also been observed.
- Prolonged ATRA treatment may cause dryness of the skin.
- Pregnancy: **ATRA is also believed to be highly teratogenic** – conduct pregnancy test to women of childbearing potential prior to starting and monthly throughout treatment until a month after treatment with tretinoin ceases. These patients must use reliable contraception while on tretinoin and for a month after. Male patients must also take appropriate contraceptive measures.
- Risk of thrombosis (venous and arterial) during the first month of treatment.
- Tetracyclines: 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
- Vitamin A: As with other retinoids, tretinoin must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated
- Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with anti-fibrinolytic agents such as tranexamic acid, aminocaproic acid and aprotinin - caution should be exercised when administering concomitantly
- Cross reaction possible if patient allergic to soya or peanut – risk assess

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### TREATMENT RELATED MORTALITY

5-10% in first week (mainly due to disease)

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### REFERENCES

- Cheplapharm. Tretinoin 10mg capsules Summary of Product Characteristics. Last updated 14/10/2021. Accessed on 2/11/2021 via <http://www.medicines.org.uk/emc>
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**REVIEW**

Name	Revision	Date	Version	Review date
Prof Vyas	Document redrafted	Sep 2016	1.2	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	1.3	Oct 2021
Yen Lim, Haematology Pharmacist. Andy Peniket, Consultant Haematologist NSSG Myeloid Group	Annual protocol meeting. Change to duration of allopurinol.	Nov 2021	1.4	Nov 2023

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