# Initial management of suspected acute promyelocytic leukaemia

**Introduction:**

A new diagnosis of acute promyelocytic leukaemia (APL) is a medical emergency. Even clinically stable patients are at risk of acute deterioration and real-world data indicate a 14% mortality rate during the initial hospital admission (27% in high-risk patients)[1]. Patients are at risk of acute life-threatening complications, including spontaneous haemorrhage secondary to disseminated intravascular coagulopathy (DIC), and differentiation syndrome. It is imperative that treatment and appropriate supportive care measures are implemented as soon as possible.

The diagnosis of APL is normally suggested by the presence of the characteristic morphology on blood film and confirmed by the presence of the *PML/RARA* genetic translocation. Patients often present with bleeding symptoms or sepsis related to the underlying diagnosis, but can also be relatively well at presentation. This guideline is adapted from the European LeukemiaNET guideline[2].

**Suspected APL on blood film**

- The on-call Laboratory BMS should immediately contact the on-call Specialist Registrar or Consultant Haematologist through switchboard.
- The patient should be reviewed by a Consultant Haematologist, or Senior Registrar, as soon as possible.
- Urgent blood tests should be sent: FBC, UE, LFT, Coagulation Screen, D-dimer, CRP +/- blood cultures if infection is suspected.
- Urgent diagnostic blood tests should be sent to North Bristol BHODS (Bristol Haemato-Oncology Diagnostic Service): FISH for *PML/RARA*, PCR for *PML/RARA* and diagnostic flow cytometry. Send 2x EDTA (purple top) and 1 x Lithium Heparin (green top).
- Samples should be blue lighted to Bristol and the on-call BMS at BHODS should be alerted to samples in transit.
- Treatment with ATRA should be initiated without delay. To access therapy a Consultant Haematologist should discuss the case with the on-call Pharmacist.
- If molecular studies rule out a diagnosis of APL then ATRA should be stopped.

**Management of coagulopathy**

- Treatment with ATRA should be started immediately by a Consultant Haematologist when a diagnosis of APL is suspected.
- Transfusions of cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately upon suspicion of the diagnosis, and then daily or more than once a day if needed, to maintain the fibrinogen concentration above 1.50, the platelet count above 50 x $10^9$/L, and the INR below 1.5.

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- Platelet counts, routine coagulation screening tests (PT, APTT and fibrinogen) and D-dimer should be monitored at least daily and more frequently if required, until disappearance of all clinical and laboratory signs of coagulopathy.
- The use of heparin and tranexamic acid is not recommended.
- Central venous catheterization, lumbar puncture, and other invasive procedures (eg, bronchoscopy) should be avoided before and during remission induction therapy due to high risk of haemorrhagic complications. Diagnostic bone marrow biopsy is normally not required.

**Low/intermediate risk disease, White Cell Count (WCC) ≤ 10 x $10^9$/L**

- Initiate ATRA and correct coagulopathy immediately.
- If the patient is deemed clinically unstable a consultant-to-consultant referral to Department of Critical Care (DCC) should be organised and transfer arranged.
- If the patient is deemed clinically stable by a Consultant Haematologist, then arrangements should be made to transfer the patient to Rendcomb ward at Cheltenham General Hospital. This should be done URGENTLY and ideally aim to transfer within normal working hours of 09:00-17:00.
- If patient is not bleeding blood product replacement should not delay hospital transfer. Transfusion should be organised to commence immediately following transfer.
- The patient will normally be managed with the standard treatment protocol for ATRA plus Arsenic trioxide (ATO). Use of ATO should be restricted to cases confirmed to be *PML/RARA* positive on genetic tests.

**High risk disease, WCC > 10 x $10^9$/L**

- If deemed unstable, patient should be urgently reviewed by DCC following consultant-to-consultant referral (either GRH or CGH depending on site of admission). Patient should initiate appropriate urgent treatment on DCC and only transfer to a Haematology ward bed once deemed stable.
- If patient presents to GRH and is deemed fit for transfer, then an urgent blue light transfer to CGH for a Haematology bed should be organised.
- Initiate ATRA immediately. Consider initiating ATRA at GRH if practical, otherwise co-ordinate treatment to initiate as soon as patient arrives in CGH.
- Correct coagulopathy immediately. If patient is not bleeding then blood product support should not delay transfer to CGH. Appropriate transfusion support should be co-ordinated to commence immediately following transfer.
- The patient is at high risk of acute differentiation syndrome. The patient should start urgent cytoreductive therapy with idarubicin 12 mg/$m^2$ prescribed by a consultant Haematologist.
- Idarubicin should be dosed and prescribed on Chemocare as soon as feasible and pharmacy alerted to minimise processing and manufacturing time.

- If high risk APL is suspected, idarubicin treatment should not be delayed waiting for genetic confirmation.
- Start dexamethasone 10 mg IV twice daily as prophylaxis against differentiation syndrome.
- If the patient is too unwell to transfer between sites during the weekend or bank holiday, then provision should be made for a nurse trained in delivering cytotoxic chemotherapy to deliver treatment to the patient on DCC in GRH.
- The patient will normally be managed with the standard treatment protocol for AIDA (ATRA + Idarubicin).

**Management of suspected differentiation syndrome**

Differentiation syndrome is a potential complication when initiating ATRA therapy in patients with APL. It presents as acute end organ damage with peripheral oedema, hypotension, acute renal failure, and interstitial lung infiltrates.

- Corticosteroids (10 mg of dexamethasone IV twice daily) should be started immediately at the earliest clinical suspicion of incipient APL differentiation syndrome; once the syndrome has resolved, steroids can be discontinued and ATO/ATRA recommenced.
- Temporary discontinuation of differentiation therapy (ATRA or ATO) is indicated only in case of severe APL differentiation syndrome.
- If not already initiated, patient should be started on cytoreductive therapy (either oral hydroxycarbamide or idarubicin depending on level of clinical concern).

**CONTACTS**

- **Haematology Consultant**: If out of hours, contact the on-call Haematology Consultant via Switchboard
- **Department of Critical Care (DCC):** contact Acute Care Response Team (ACRT) via bleep 1700, or contact the on-call DCC consultant via switchboard depending on level of clinical concern
- **Pharmacy:** on-call out of hours via Switchboard.

**References**


1. Bewersdorp JP, Prozora S, Podoltsev NA, *et al.* Practice patterns and real-life outcomes for patients with acute promyelocytic leukemia in the United States. *Blood Adv.* 2022;6(2):376-385.
2. Sanz MA, Fenaux P, Tallman MS, *et al.* Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood.* 2019;133(15):1630-1643.