Acute Promyelocytic Leukaemia
PI-APML #1 Protocol

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Use of this protocol is at the discretion of the treating physicians in Fiji depending on the local perception of their ability to manage therapy delivery and supportive care in the local setting.

ACUTE PROMYELOCYTIC LEUKAEMIA

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Acute Promyelocytic Leukaemia (APML)

- characterised by clinical (refractory coagulopathy), morphological (promyelocytic differentiation arrest) and cytogenetic t(15;17)(q21;q11) with production of PML-RARα fusion gene.
- considerable progress made over the last 10 years with introduction of all trans retinoic acid (ATRA), a biologic response modifier) which induces differentiation of the leukaemic cells into mature granulocytes. The introduction of ATRA in APML has led to a dramatic improvement in outcome.
- APML is the most curable subtype of AML in the developed world with CR 80-90% and 5yr OS 70-80%
- 15% cases of AML < 45 yrs age

Diagnosis / Investigations

- FBC - cytopenias / peripheral film with abnormal promyelocytes
- Coagulation screen - PR / APTT / Fibrinogen / D-dimers / Exclude DIC
- Urea, electrolytes, creatinine, uric acid, liver function tests
- Bone marrow biopsy
  - morphology abnormal promyelocytes, microgranular variant
  - cytochemistry
  - immunophenotyping including PML antibody test
  - cytogenetics t(15;17)(q21;q11)
    variants include:
    t(11;17)(q23;q11)
    t(5;17)(q32;q11)
    t(11;17)(q13;q11)
  - FISH t(15;17)(q21;q11) / PML-RARα
  - RT-PCR PML-RARα fusion gene

  For Fiji : send unstained slides for FISH t(15;17) to CHOC, c/- Christchurch Hospital.

Risk profile

- Low risk WCC < 10 x 10^9/L and Platelets > 40 x 10^9/L
- Intermediate risk WCC < 10 x 10^9/L and Platelets < 40 x 10^9/L
- High risk WCC > 10 x 10^9/L
- Major risk factors are age and WCC at presentation

ACUTE PROMYELOCYTIC LEUKAEMIA

Treatment

- historically APML was associated with particular sensitivity to anthracyclines and subsequently no difference in CR rates between daunorubicin or idarubicin alone or daunorubicin or idarubicin and cytarabine were observed.
- the use of ATRA in conjunction with anthracycline chemotherapy is now considered standard induction therapy with:
  -Complete remission 70-95%
  -Induction mortality 10%
  -Relapse 20-30%
- ATRA should be administered as soon as possible to patients with newly diagnosed coagulopathy and suspected acute leukaemia ? promyelocytic (beware of RAS - see later)
- there appears also to be no role for cytarabine in consolidation treatment with an ATRA and anthracycline combination just as effective.
- maintenance therapy with ATRA and low dose chemotherapy has been shown in randomised trials to be critical in reducing the relapse rate.

Treatment Protocol for patients with Body surface area >0.6m2
For patients with Body surface area <0.6m2 refer page 6

INDUCTION

- **ATRA** 25mg / m^2 / day PO in 2 divided doses (maximum dose 80 mg / day)
- Until complete remission or for a maximum of 90 days
- **Daunorubicin** 50 mg / m^2 Daily IV bolus over 15-20 minutes Days 2, 4, 6, 8 (4 doses)
- **Dexamethasone** 5.8mg/m2/dose PO/IV 12 hourly (maximum 10mg/dose) ATRA syndrome treatment or prophylaxis when WCC > 5 x 10^9/L. Continue until WCC < 5 x 10^9/L
- **Allopurinol** 100mg/m2/dose TDS (check renal function)

Bone marrow aspirate at end of induction
Stop Allopurinol after induction phase once risk of TLS gone (WCC <5 x 10^9/L.)

CONSOLIDATION
2 cycles at monthly intervals

CYCLE # 1

- **Daunorubicin** 50 mg / m^2 IV Daily Days 1 (single dose only)
- **ATRA** 25mg / m^2 / day PO Days 1 – 15 in 2 divided doses (max. dose 80 mg / day)
- Bone marrow aspirate for review at end of consolidation #1 – if not in morphological remission then family should be counselled and transferred to palliative care.
  For Fiji- if there is doubt as to whether remission is present then sample should be sent to Christchurch Hospital for FISH testing.

CYCLE # 2

- **Daunorubicin** 50 mg / m^2 IV Daily Days 1 (single dose only)
- **ATRA** 25mg / m^2 / day PO Days 1 – 15 in 2 divided doses (max. dose 80 mg / day)

MAINTENANCE

2 year maintenance programme for patients who are negative for PML-RARα fusion gene by RT-PCR.

- **6-Mercaptopurine** 75 mg / m^2 PO daily (50 mg tablet size)
- **Methotrexate** 20 mg / m^2 PO weekly
- **ATRA** 25 mg / m^2 / day PO Days 1 – 15 in 2 divided doses Every 3 months (max. dose 80 mg / day)
- may need to reach target dose slowly due to excessive myelosuppression / hepatotoxicity e.g. commence 6-Mercaptopurine at 50 mg / m^2 daily initially for 2 weeks then increase dose as tolerated.
- Dose Modification
  -↓ 6-Mercaptopurine / Methotrexate if ANC < 1.0 x 10^9/L
  - stop 6-Mercaptopurine / Methotrexate if ANC < 0.5 x 10^9/L
  (refer PI ALL 2 protocol- section 9.3)

SUPPORTIVE CARES –continue for at least the first 7 days unless otherwise stated.

- Red blood cells - maintain Hb > 90 g/L
- Platelets - induction : maintain Plts > 30 x 10^9/L until coagulopathy resolved
  - consolidation : maintain Plts > 10 x 10^9/L
- **Coagulopathy**
  - elements of DIC and hyperfibrinolysis may be life threatening at presentation
  - exacerbated by chemotherapy / dampened by ATRA after 48 – 72 hrs
  - monitor PR / APTT / Fibrinogen / D-dimers closely on BD basis for 72 hours
  - maintain fibrinogen > 1.0 g/L
  - correct hypofibrinogenaemia aggressively with cryoprecipitate
    - e.g. 0.5 – 1.0 g/L 1 unit cryoprecipitate
    - < 0.5 g/L 2 units cryoprecipitate
  - correct prolonged APTT / PR with FFP as required
  - reactivation described at Days 7 – 14 of induction therapy
- **Fever / Sepsis** - refer Febrile Neutropaenia protocol
- **ATRA (Retinoic acid, RAS) syndrome** (see the section at the end of this protocol)
- Daily cares
  - FBC initially twice daily
  - urea/ electrolytes/ creatinine daily
  - Coagulation profile twice daily
  - Patient weighs twice daily
  - O2 saturations twice daily

ATRA TOXICITY

- ATRA is generally well tolerated
- Patients should have weekly Creatinine and LFTs as a minimum and 3 monthly Lipid studies after the initial 7 day period
- See below for ATRA (Retinoic acid, RAS) syndrome

ATRA (Retinoic acid, RAS) syndrome

- major toxicity of ATRA
- cardiorespiratory distress syndrome (similar to ARDS) and manifest by:

- Fever
- Weight gain
- Respiratory distress
- Interstitial pulmonary infiltrates
- Pleural and pericardial effusions
- +/- Episodic hypotension
- +/- Acute renal failure

- potential difficulty in obtaining an accurate diagnosis in patients with chemotherapy related sepsis and fluid overload.
- incidence 15 - 25% with ATRA alone but appears reduced with concurrent early administration of chemotherapy (5-10%).
- mortality is variable at 4-29% of RAS patients.
- difficult to identify factors that predict for RAS.
- Steroids are used in preventing RAS and their role in treatment of the established syndrome is clear. Dexamethasone reduces mortality in established RAS. Recommend the administration of Dexamethasone 0.25mg/kg/dose BD (maximum10 mg/dose) PO/ IV Q 12 hourly as treatment for RAS or as prophylaxis when WCC > 5 x 10 x 10^9/L.
- If suspect patient has RAS on basis of criteria listed above then stop ATRA and commence Dexamethasone at above dose.
- ATRA can be restarted when the RAS has resolved at 75% initial dose with an increase to the full ATRA dose after 7 days if there has been no recurrence of RAS symptoms / signs.
- not associated with use of ATRA in maintenance therapy

Treatment Protocol For patients with Body surface area <0.6m2

INDUCTION

- **ATRA** 25mg/ m^2 /day PO in 2 divided doses
- Until complete remission or for a maximum of 90 days
- **Daunorubicin** 1.7mg/kg/dose Daily IV bolus over 15-20 minutes Days 2, 4, 6, 8 (4 doses)
- **Dexamethasone** 0.25mg/kg/dose BD PO/IV ATRA syndrome treatment or prophylaxis when WCC > 5 x 10^9/L. Continue until WCC < 5 10 x 10^9/L
- **Allopurinol** PO daily 100mg/m2/dose TDS (check renal function)

Bone marrow aspirate for review at end of Induction

CONSOLIDATION
2 cycles at monthly intervals

CYCLE # 1

- **Daunorubicin** 1.7mg/kg/dose IV Daily Day 1 (single dose only)
- **ATRA** 25mg/m^2 /day PO Days 1 – 15 in 2 divided doses

Bone marrow aspirate for review at end of consolidation # 1 – if not in morphological remission then family should be counselled and transferred to palliative care. If there is doubt as to whether remission is present then sample should be sent to Christchurch Hospital for FISH testing.

CYCLE # 2

- **Daunorubicin** 1.7mg/kg/dose IV Daily Day 1 (single dose only)
- **ATRA** 25mg/m^2 /day PO Days 1 – 15 in 2 divided doses

MAINTENANCE
2 year maintenance programme for patients who are in morphological remission

- **6-Mercaptopurine** 75 mg / m^2 PO daily (50 mg tablet size)
- **Methotrexate** 20 mg / m^2 PO weekly
- **ATRA** 25 mg / m^2 / day PO Days 1 – 15 in 2 divided doses Every 3 months
- may need to reach target dose slowly due to excessive myelosuppression / hepatotoxicity from previous courses
- Dose Modification
  -↓ 6-Mercaptopurine / Methotrexate if ANC < 1.0 x 10^9/L
  - stop 6-Mercaptopurine / Methotrexate if ANC < 0.5 x 10^9/L
  (refer PI ALL 2 protocol)

Reference:
1.Da Costa Moraes CA et al. Pediatric Acute Promyelocytic leukaemia: All-transretinoic Acid therapy in a Brazilian Pediatric Hospital. J Pediatr Hematol Oncol. Vol 30, No 5, May 2008
2. COG AAML0631 study (now closed)