Updates: Guidelines for intrathecal chemotherapy

Introduction

Acute promyelocytic leukemia (APL) is a subtype of AML according to the FAB classification, but because of differences in epidemiology, treatment, prognosis and complications it is considered separately [1].

Diagnosis

The diagnosis of APL is strongly suggested by blood film appearance. Bone marrow aspiration and demonstration of a characteristic chromosomal translocation confirms the diagnosis of APL. APL is classically associated with t(15, 17), resulting in the PML-RARα gene fusion; t(11, 17) and other variant translocations involving chromosome 17 are extremely rare [1].

Prognosis & Staging

Although the prognosis in APL is generally very good, a number of negative prognostic indicators have been identified, including:

1. High WBC count (> 10 x 10⁹/L) at presentation,
2. Flt3 gene internal tandem duplication (ITD),
3. PML-RAR(S) isoform,

Patients exhibiting one or more of these characteristics are at increased risk of disease relapse and should be considered for more intensive maintenance therapy (see below).

Baseline Investigations

Most patients with acute promyelocytic leukemia (APL) should have the following baseline investigations:

- Bone marrow aspiration with cytogenetic and molecular analysis
- CBC, diff, blood film
- INR, PTT, fibrinogen, thrombin time, D-dimer
- Serum electrolytes, liver function tests
- Serum uric acid
- Group & screen
Treatment

Patients with APL have a favorable prognosis when treated with all-trans-retinoic acid (ATRA) and anthracycline-based chemotherapy [2-4]. Five-year survival rates of 70-80% have been reported with the most impressive results being seen with addition of maintenance therapy [5]. Arrangements to obtain ATRA with Ontario Drug Benefits or third party insurers should be started at the time of initial diagnosis.

The role of cytarabine in the induction and consolidation therapy of APL has been controversial. Clinical trials support the importance of anthracyclines, but have not established the utility of Ara-C either in attaining complete remission or in 4-year disease-free or overall survival. However, since ATRA became the mainstay of treatment for APL, a higher frequency of extramedullary relapse has been observed; this has been ascribed to the reduction in intensity of cytotoxic chemotherapy for APL [6]. For this reason we now include a single cycle of high dose cytarabine in the consolidation chemotherapy regimen for APL.

Remission Induction

Patients undergo induction with ATRA 45 mg/m²/day (rounded off to nearest 10mg amount) in two divided doses with meals for 28 days and daunorubicin 60 mg/m² days 6, 7, and 8. If WBC >10 x 10⁹/L at presentation, daunorubicin is given on days 1, 2, and 3. Remission is documented by bone marrow aspiration at day 28 or when counts recover (ANC > 0.5; platelet count > 100).

LP Criteria:

Patients with initial WBC > 10 x 10⁹/L (or leukemic blasts expressing CD56) should have a diagnostic LP performed on Day 10-12 of induction, after blasts have cleared from the blood, with cytarabine 70 mg given intrathecally (IT).

- If CNS is clear, cytarabine 70 mg IT should subsequently be given for additional CNS prophylaxis at the start of each consolidation, and once more at the start of maintenance therapy, i.e. 4 intrathecal injections in total
- If CSF is positive, LP + IT chemotherapy should be given twice weekly until clear

Assessment of Response

Remission is documented by bone marrow aspiration at day 28 or when counts recovers (ANC >0.5; plt >100). If blasts (including, by convention, abnormal promyelocytes) comprise <5% of marrow cellularity a patient will be considered to have responded and will proceed to consolidation. Patients who do not achieve a response will be considered to have persistent disease (see below).

It is not uncommon for molecular evaluation by RT-PCR to reveal persistent presence of PML-RAR transcripts at this stage of treatment. This does not indicate failure of induction therapy, and as long as morphological remission has been achieved, patients should proceed to consolidation therapy.

Consolidation

Two cycles of consolidation are given, each starting 5-6 weeks after the last cycle of treatment. Consolidation #1 consists of ATRA 45 mg/m²/day in divided doses x 28 days, daunorubicin 60 mg/m² x 3 days starting day 1, and cytarabine 100mg/m²/day by continuous IV infusion x 7 days, days 1-7.

The second consolidation will consist of ATRA 45 mg/m²/day x 28 days, daunorubicin 45 mg/m², days 1, 2 & 3, and cytarabine 1.5 g/m² q12h x 6 doses, days 1, 3, and 5.
MUGA scan is performed prior to each consolidation cycle. If LVEF is < 50%, substitute amsacrine 125 mg/m²/day x 3 days instead of daunorubicin.

Bone marrow aspiration should be repeated after recovery from consolidation cycle 2. At this stage PML-RAR transcripts should be undetectable. If molecular testing after the completion of consolidation therapy reveals evidence of persistent disease, bone marrow aspiration should be repeated in one week to confirm this. Patients with confirmed molecular positivity should undergo re-induction chemotherapy (see Treatment of Persistent or Recurrent Disease).

Maintenance

Maintenance therapy is given to all patients, but the intensity of maintenance therapy is adjusted according to initial WBC count. Patients exhibiting other evidence of high risk for relapse (Flt3 ITD, S-isoform of PML-RAR, CD56 expression) should also be considered for augmented maintenance therapy.

For patients with initial WBC <10 x 10⁹/L: Patients receive ATRA maintenance 45 mg/m²/day in two divided doses with meals for 1 week every second week for 9 months [5]. Molecular monitoring by quantitative RT-PCR is performed at 3-month intervals for 2 years.

For patients with initial WBC >10 x 10⁹/L: Patients with higher initial WBC counts are at higher risk for relapse, and therefore receive a maintenance regimen of higher intensity and longer duration. The high-risk maintenance regimen comprises:

1. ATRA 45 mg/m²/day in two divided doses with meals for 15 days q2months (i.e. every second cycle) for 21 cycles,
2. 6-mercaptopurine 75 mg/m²/day po x 21 days, repeated q28 days for 21 cycles,
3. Methotrexate 20 mg/m²/day po once weekly through 21 4-week cycles.

This maintenance regimen can cause significant toxicity and patients must be monitored monthly (CBC, liver enzymes, creatinine). Dose adjustments are made as follows:

- If absolute neutrophil count 1.0 -2.0 x 10⁹/L, reduce doses of 6-MP and MTX by 50%; if ANC at next cycle > 2.0 x 10⁹/L, increase to 80% of original dose,
- If ANC < 1.0 x 10⁹/L, delay next cycle until ANC recovers, then reduce doses of 6-MP and MTX for next cycle by 20%,
- If AST or ALT >4 x normal, or bilirubin>1.5 x normal, reduce doses of 6-MP and MTX by 20%,
- If AST or ALT >8 x normal or bilirubin >3 x normal hold 6-MP, MTX, and ATRA.

Monitoring

Molecular monitoring of high-risk patients is performed by quantitative RT-PCR monitoring of bone marrow aspirates at 3-month intervals for 3 years.

Molecular monitoring may reveal the re-emergence of PML-RAR expression during or following maintenance therapy despite normal peripheral blood counts and morphology. A newly positive molecular result necessitates a repeat bone marrow aspiration for molecular testing as soon as feasible; confirmation of molecular relapse on the second molecular evaluation should lead to re-induction therapy (see Treatment of Persistent or Recurrent Disease).
Treatment of Persistent or Recurrent Disease

Patients with molecular or morphologic evidence of persistent or recurrent disease should be re-induced with:
- Arsenic trioxide 0.15 mg/kg IV daily until CR
- OR
- ATRA 45 mg/m²/day in 2 divided doses x 28 days
- Amsacrine 100 mg/m² IV daily, days 1-5
- Cytarabine 200 mg/m² continuous IV infusion daily x 7 days (100 mg/m² if age >60)
- OR
- Mylotarg 9 mg/m² over 2 hours on days 1 and 15
- ATRA 45 mg/m²/day in 2 divided doses x 28 days

Successful re-induction should be followed by consolidation with ATRA 45 mg/m² day x 28 days, cytarabine 1.5 g/m² iv q12h x 6 doses, days 1, 3, and 5, and amsacrine 100 mg/m² daily x 2 days with intent to proceed to matched related sibling donor stem cell transplant or autologous stem cell transplant from an RT-PCR negative graft.

Special Considerations

(a) **DIC**: Patients with APL are at increased risk for DIC [7]. Patients with evidence of DIC prior to initiation of therapy should have ATRA started prior to chemotherapy and should receive cryoprecipitate to keep fibrinogen > 1.0.

(b) **ATRA Syndrome**: The ATRA syndrome is characterized by weight gain, fluid retention, pulmonary infiltrates and effusions. It can be treated effectively by dexamethasone 10 mg BID IV for at least 3 days [8]. Patients should have daily weights measured and should undergo chest x-ray for even minor respiratory complaints early in the course of treatment. Early intervention for ATRA syndrome improves outcome. Prophylactic treatment with dexamethasone as described above is recommended for patients with presenting WBC > 10 x 10⁹/L.

(c) **CNS Prophylaxis**: The risk of CNS relapse of APL is higher in patients with high WBC at presentation. Patients with WBC > 10 x 10⁹/L at presentation should have a diagnostic lumbar puncture and intrathecal instillation of 70 mg cytarabine on day 10-12 of induction. If the CSF is clear, cytarabine 70 mg IT should be given prophylactically at the start of each consolidation cycle and once more at the start of maintenance therapy for a total of 4 doses. If the CSF is positive on any LP, IT chemotherapy should be given twice weekly until clear.
**APL Algorithm**

**INDUCTION**
ATRA 45 mg/m²/day x 28 days
Daunorubicin 60 mg/m² days 6, 7, 8
(+ CNS prophylaxis if WBC >10)

**CONSOLIDATION #1**
ATRA 45 mg/m²/day x 28 days
Daunorubicin 60 mg/m² days 1, 2, 3
Cytarabine 100 mg/m²/d x 7

**CONSOLIDATION #2**
ATRA 45 mg/m²/day x 28 days
Daunorubicin 45 mg/m² days 1, 2, 3
Cytarabine 1.5 mg/m² IV q12h x 6 doses, days 1, 3, 5

High-Risk

**MAINTENANCE**
ATRA 45 mg/m²/d x 15 d q 2 months
6 MP 75 mg/m² x 21 d q 1 month
MTX x 20 mg/m² once weekly x 21 months

Standard-Risk

**MAINTENANCE**
ATRA 45 mg/m²/day x 7 days
Every second week x 9 months

**MONITORING**
BM for PML-RAR every 3 months for 3 years

**MONITORING**
BM for PML-RAR every 3 months x 2 years
6 months x 3 years
References