Leukemia Site Group – Acute Promyelocytic Leukemia

Date Guideline Created: October 2011   Author: Dr. Andre Schuh

1. INTRODUCTION  

2. PREVENTION  

3. SCREENING AND EARLY DETECTION  

4. DIAGNOSIS  

5. PATHOLOGY  

6. MANAGEMENT  

6.1 MANAGEMENT ALGORITHMS  
6.2 TREATMENT REGIMENS  
6.3 RADIATION THERAPY  
6.4 OTHER THERAPY  
6.5 ONCOLOGY NURSING  

7. SUPPORTIVE CARE  

7.1 PATIENT EDUCATION  
7.2 PSYCHOSOCIAL CARE  
7.3 SYMPTOM MANAGEMENT  
7.4 CLINICAL NUTRITION  
7.5 PALLIATIVE CARE  

8. FOLLOW-UP CARE  

9. REFERENCES  

Last Revision Date – August 19, 2019
1. Introduction
These guidelines relate to the management of acute promyelocytic leukemia (APL) as currently practiced at Princess Margaret Cancer Centre. While a subtype of acute myeloid leukemia (AML), the unique biological and clinical features (coagulopathy, thrombotic events, differentiation syndrome), and good overall prognosis, of APL warrant its discussion as a distinct entity.

2. Prevention
Preventive strategies are generally not available for APL. However, heightened awareness and ongoing surveillance, as appropriate, may be considered in specific situations (see 3. below).

3. Screening and Early Detection
Screening and early detection is generally not relevant in APL. However, heightened awareness and ongoing surveillance, as appropriate, may be considered in specific clinical settings associated with the development of AML, including APL. These include the treatment of other malignancies with chemotherapy, and in particular, with alkylating agents and with topoisomerase II inhibitors, and with radiotherapy, and “pre-leukemic” conditions, such as myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs).

4. Diagnosis
The comprehensive diagnosis of APL is based on the examination of the peripheral blood and bone marrow both morphologically and by flow-cytometry +/- immunocyto- and immunohistochemical studies, as appropriate, and by additional cytogenetic and molecular studies, ideally performed on the bone marrow. In cases in which bone marrow aspiration yields an adequate sample, additional bone marrow biopsy, while complementary, is not essential for diagnosis. In cases in which the aspirate is unsuccessful or inadequate, however, biopsy is essential.

5. Pathology
Hematopathology (including flow cytometry), cytogenetics, and molecular studies contribute to the comprehensive diagnosis of APL.

5i. Hematopathology
APL corresponds to the M3 variant of the French-American-British (FAB) classification (1976, 1985, 1991), and features distinctive morphology, cytochemistry, immunophenotype and cytogenetics.

Table 1. FAB Classification of AML
<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated acute myeloblastic leukemia; AML with minimal</td>
</tr>
<tr>
<td></td>
<td>differentiation</td>
</tr>
<tr>
<td>M1</td>
<td>Acute myeloblastic leukemia with minimal maturation; AML without</td>
</tr>
<tr>
<td></td>
<td>maturation</td>
</tr>
<tr>
<td>M2</td>
<td>Acute myeloblastic leukemia with maturation</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia (APL)</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukemia</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroid leukemia</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukemia</td>
</tr>
</tbody>
</table>

In the more recent **World Health Organization (WHO) classification** (2002, 2008, 2016), APL falls into the category AML with recurrent genetic abnormalities.

**Table 2. WHO Classification of Myeloid Neoplasms and Acute Leukemia (2016)**

<table>
<thead>
<tr>
<th>AML and related neoplasms</th>
<th>Entities</th>
</tr>
</thead>
</table>
| AML with recurrent genetic abnormalities | • AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*  
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*  
• APL with *PML-RARA*  
• AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*  
• AML with t(6;9)(p23;q34.1); *DEK-NUP214*  
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*  
• AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*  
• **Provisional entity: AML with BCR-ABL1**  
• AML with mutated *NPM1*  
• AML with biallelic mutations of *CEBPA*  
• **Provisional entity: AML with mutated *RUNX1** |
| AML with myelodysplasia-related changes |                                                                                        |
| Therapy-related myeloid neoplasms |                                                                                        |
| AML, Not Otherwise Specified (NOS) | • AML with minimal differentiation  
• AML without maturation  
• AML with maturation  
• Acute myelomonocytic leukemia  
• Acute monoblastic/monocytic leukemia  
• Pure erythroid leukemia  
• Acute megakaryoblastic leukemia  
• Acute basophilic leukemia |
**Acute panmyelosis with myelofibrosis**

**Myeloid Sarcoma**

**Myeloid proliferations related to Down syndrome**
- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia associated with Down syndrome

**Blastic plasmacytoid dendritic cell neoplasm (BPDCN)**
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); **BCR-ABL**
- MPAL with t(v;11q23.3); **KMT2A** rearranged
- MPAL, B/myeloid, NOS
- MPAL, T/myeloid, NOS

**Acute leukemias of ambiguous lineage**

**Immunophenotype:**

Classical APL features a distinctive immunophenotype defined by flow cytometry: the CD13+, CD33+, CD34-, HLA-DR- pattern is classic. In addition, APL is often CD15-, CD11a-, CD11b-, CD11c-, CD18- (a-subunit of CD11a, b, c), CD66b- and CD66c-, and can be CD56+.

**5ii. Cytogenetics**

Greater than 98% of cases of APL carry the specific t(15;17)(q22;q21), in which fusion between the **PML** and **RARα** genes occurs, resulting in the impairment of retinoic acid-dependent myeloid gene expression.

Cytogenetically, APL falls in the “favourable” or “good” cytogenetic risk group. Notably, the presence of additional cytogenetic abnormalities does not influence APL’s good prognosis.

**Table 3. AML Cytogenetic Risk Group (SWOG and MRC)**

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>SWOG</th>
<th>Revised MRC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>N=609</td>
<td>N=5876</td>
</tr>
<tr>
<td>Favourable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inv(16)/t(16;16)/del(16q); t(15;17) with/without secondary abn; t(8;21) w/o del(9q) or complex karyotypes</td>
<td>N=121 (20%)</td>
<td>inv(16)/t(16;16)/del(16q); t(15;17); t(8;21) with/without secondary abn</td>
</tr>
<tr>
<td></td>
<td>OS₅₅ 55%</td>
<td>OS₁₀₉ 69%</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal; +8; +6; -Y; del(12p)</td>
<td>N=278 (46%)</td>
<td>Entities not classified as favorable or adverse</td>
</tr>
<tr>
<td></td>
<td>OS₅₅ 38%</td>
<td>OS₁₀₉ 33-38%</td>
</tr>
<tr>
<td>Unfavorable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(5q)-5; -7/del(7q); abn 3q; 9q; 11q; 20q;</td>
<td>N=184 abn(3q) [excl t(3;5)(q21<del>25;q31</del>35)];</td>
<td>N=955</td>
</tr>
</tbody>
</table>

Last Revision Date – August 19, 2019
<table>
<thead>
<tr>
<th>21q; 17p; t(6;9); t(9;22); complex (≥ 3 unrelated abn)</th>
<th>(30%)</th>
<th>inv(3)(q21q26)/t(3;3)(q21;q26); add(5q); del(5q)/-5; add(7q); -7/ del(7q); t(6;11)(q27;q23); t(10;11)(p11<del>13;q23); t(11q23) [excl t(9;11)(p21</del>22;q23) &amp; t(11;19)(q23;p13)]; t(9;22)(q34;q11); -17/abn(17p); complex (≥ 4 unrelated abn); monosomy karyotype</th>
<th>(16%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS5y 11%</td>
<td>inv(3)(q21q26)/t(3;3)(q21;q26); add(5q); del(5q)/-5; add(7q); -7/ del(7q); t(6;11)(q27;q23); t(10;11)(p11<del>13;q23); t(11q23) [excl t(9;11)(p21</del>22;q23) &amp; t(11;19)(q23;p13)]; t(9;22)(q34;q11); -17/abn(17p); complex (≥ 4 unrelated abn); monosomy karyotype</td>
<td>OS10y 12%</td>
<td></td>
</tr>
</tbody>
</table>

*a* Age < 56 years; *b* Age ≤ 59 years

APL can also be associated with non-PML translocations involving RARα albeit rarely. These include, t(11;17)(q23;q21) involving PLZF (<1% of cases), t(5;17)(q35;q21) involving NPM (<0.5% of cases), t(11;17)(q13;q21) involving NuMA, and t(17;17)(q11;q21) involving STAT5, among others.

APL-related translocations can be detected by karyotypic analysis, and also by FISH analysis using an RARα break-apart probe.

5iii. Molecular

Based on a high index of suspicion (distinctive morphology and clinical presentation [e.g. coagulopathy or thrombosis]), the diagnosis of APL is usually confirmed by PCR analysis, although standard PCR will detect only t(15;17).

While, the RARα breakpoint always lies within intron 2, the PML breakpoint can lie in intron 3 (BCR3; S form), intron 6 (BCR1; L form) and exon 6 (BCR2; V form).

Molecular testing also plays an important role in ongoing, post-remission, APL minimal residual disease (MRD) assessment (see 6. and 8. below). Specifically, after count recovery following an ATRA and ATO based-induction therapy, a proportion of patients will remain PCR positive although their marrows are in morphological CR. However, the presence of measurable cytogenetic or PML-RARα levels does not have prognostic or therapeutic implications at this time point. After the completion of consolidation, however, ~95+% of patients have become PCR negative. Those few who remain PCR positive at this point require further treatment for persistent disease (see 6.2.2 below).

Similarly, during long-term molecular follow-up of patients in CR, patients who convert from PCR negative to PCR positive status should be treated for recurrent disease (see 6.2.2 below).

6. Management

6.1 Management Algorithms
Based on an assessment of prognostic factors (Table 4), an appropriate individualized treatment plan is chosen. Patients with low-risk (i.e. WBC count ≤ 10 × 10⁹/L, platelet count > 40 × 10⁹/L), intermediate-risk (i.e. WBC count ≤ 10 × 10⁹/L, platelets ≤ 40 × 10⁹/L), and high-risk (i.e. WBC count > 10 × 10⁹/L) APL have distinctive relapse-free survival curves. However, due to its high curability, APL is usually treated aggressively, even in very elderly patients.

**Table 4. Prognostic Factors in APL**

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good risk</td>
</tr>
<tr>
<td>• t(15;17) abnormality</td>
</tr>
<tr>
<td>• WBC ≤ 10 x 10⁹/L</td>
</tr>
<tr>
<td>• Platelet &gt; 40 x 10⁹/L</td>
</tr>
<tr>
<td>Poor risk</td>
</tr>
<tr>
<td>• t(11;17) abnormality due to ATRA and arsenic resistance</td>
</tr>
<tr>
<td>• WBC &gt; 10 x 10⁹/L</td>
</tr>
<tr>
<td>• CD56-positive myeloblasts</td>
</tr>
<tr>
<td>• PML breakpoint (BCR2 and BCR3 may confer worse outcome)</td>
</tr>
</tbody>
</table>

Start all-\textit{trans} retinoic acid (ATRA; tretinoin) upon the first suspicious of APL. Early initiation of ATRA may prevent lethal bleeding. If molecular and/or cytogenetic (or FISH) testing do not confirm APL, discontinue ATRA and continue therapy as for AML.

Treatment protocols for newly diagnosed APL patients are listed in 6.2 below. Induction therapy should not be modified based on the presence of leukemia cell characteristics that have been considered to be poor risk features (e.g. FLT3 mutations, CD56 expression and BCR3 \textit{PML-RARα} isoforms).

Treatment approaches to relapsed/refractory disease are found in 6.2 below.

Treatment of the frequently-associated coagulopathy, thrombosis, and differentiation syndrome is found in 6.4 below.

Ongoing MRD monitoring is found in 6.4 below.

Autologous and allogeneic SCT indications are found in 6.4 below.

**6.2 Treatment Regimens**

Treatment is defined primarily by presentation WBC, and patient age.

Newly diagnosed patients are considered in section 6.2.1. Non-responding and relapsed/refractory disease is considered in section 6.2.2.

**6.2.1 Newly diagnosed APL Patients – Induction, Consolidation, Maintenance**

Since the availability of arsenic trioxide and ATRA for newly diagnosed patients with APL, chemotherapy is rarely used (see below 6.2.1.3 for newly diagnosed APL patients).
6.2.1.1 Low-intermediate risk APL (WBC < 10 x 10^9/L) – LoCoco Protocol

Arsenic trioxide (ATO) plus ATRA daily until complete remission (CR) or for a maximum of 60 days, then ATO 5 days/week, 4 weeks on 4 weeks off, for a total of 4 courses and ATRA 2 weeks on and 2 weeks off for a total of 7 courses. The schema is detailed below.

**Figure 1. Schema of Low-Intermediate Risk APL (LoCoco) Protocol**

**Induction Regimen:**
- all-trans retinoic acid (ATRA) 45mg/m²/day in 2 divided doses (rounded to the nearest 10 mg increment) starting on Day 1. ATRA treatment will be continued until hematological CR or for a maximum of 60 days.
- Arsenic trioxide (ATO) 0.15 mg/kg IV over 2 hours daily starting on Day 1. ATO will be continued until hematological CR or for a maximum of 60 days.
- Start hydroxyurea if WBC is > 10 x 10^9/L during treatment (and discontinue when WBC drops to > 10 x 10^9/L).
- Start prophylactic dexamethasone 10 mg IV q12h if WBC > 10 x 10^9/L (to prevent differentiation syndrome)

**Consolidation Regimen:**
- ATRA 45 mg/m²/day will be administered orally in 2 equally divided doses (rounded to the nearest 10 mg increment). Treatment will be administered for 2 weeks on 2 weeks off and for a total of 7 cycles (last cycle administered on weeks 25 - 26).
- ATO 0.15 mg/kg IV over 2 hours daily for 5 days every week. Treatment will be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles (last cycle administered on weeks 25 - 28).

Patients who do not achieve molecular remission at the end of the entire consolidation programme will be considered as molecular resistant.

**Supportive Care:**
- QTc prolongation - close monitoring of the EKG (i.e. baseline and at minimum twice weekly) and of the electrolytes (i.e. minimum at least twice weekly) is necessary during treatment with ATO. In particular, the Mg²⁺ and K⁺ levels should always be kept in the high-normal range (i.e. ~0.9 mmol/L and ~4 mmol/L, respectively), taking in consideration possible concomitant treatments that deplete electrolyte levels (e.g.
amphotericin B, furosemide etc.) and avoidance of drugs that can prolong QTc interval (e.g. azoles).

Management of QTc prolongation:
- As per above
- Hold ATO if QTc > 500 msec and administer ATO when QTc < 500 msec or as directed by electrophysiology service (EPS) or cardiology service

- Differentiation syndrome – seen with both ATRA and ATO. Defined by the presence of unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusion, with or without hyperleukocytosis. No single sign or symptom is diagnostic of the syndrome. Given the life-threatening character of a full-blown syndrome, it is recommended that the prophylactic and therapeutic measures indicated below be undertaken to manage suspected differentiation syndrome (e.g. unexplained respiratory distress).

Management of suspected differentiation syndrome:
- may need temporary discontinuation of ATRA and/or ATO in cases of severe differentiation syndrome;
- initiation of DEXAMETHASONE 10 mg q12 hrs IV until disappearance of symptoms and signs, and for a minimum of 3 days;
- furosemide when clinically required

- Hepatotoxicity – seen by ATRA and ATO. Characterized by increase in serum bilirubin and/or AST and/or alkaline phosphatase > 5 X the normal upper level (ULN).

Management of hepatotoxicity:
- temporarily discontinue ATRA and/or ATO.
- As soon as serum bilirubin and/or AST and/or alkaline phosphatase is < 4 x ULN, treatment with ATRA and/or ATO will be resumed at 50% of the previous dose during the first 7 days. In absence of worsening of the previous toxicity, ATRA and/or ATO should be resumed at full dosage. In case of reappearance of ATRA and/or ATO hepatotoxicity, the drug must be definitely discontinued.

- Pseudotumor cerebri – seen with ATRA. Characterized by presence of severe headache with nausea, vomiting, and visual disorders.

Management of pseudotumor cerebri (idiopathic intracranial hypertension):
- temporarily discontinue ATRA
- administer opiates
- administer acetazolamide
- as soon as the symptoms and the patient clinical conditions improve, the treatment with ATRA will be resumed at 50% of the previous dose during the first 7 days after the amelioration of pseudotumor cerebri. Thereafter, in
absence of worsening of the previous toxicity, ATRA should be resumed at full dosage.

- **Myelosuppression** –

Management of myelosuppression:

- For significant myelosuppression (i.e. ANC < 1 x 10⁹/L, platelets < 50 x 10⁹/L for > 5 weeks after start of a course) and no evidence of morphologic disease, hold ATRA and ATO to allow for PB count recovery as ATO can be associated with significant myelosuppression or 1 dose level reduction as noted below. If myelosuppression lasts > 49 days or occurs on 2 consecutive courses, repeat bone marrow aspirate with specimens for RT-PCR. In case of Molecular CR (CRm) reassume treatment at one dose level lower than previously used dosage.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>ATO (mg/kg)</th>
<th>ATRA (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose Level 0</td>
<td>0.15</td>
<td>45</td>
</tr>
<tr>
<td>-1</td>
<td>0.11</td>
<td>37.5</td>
</tr>
<tr>
<td>-2</td>
<td>0.10</td>
<td>25</td>
</tr>
<tr>
<td>-3</td>
<td>0.075</td>
<td>20</td>
</tr>
</tbody>
</table>

**6.2.1.2 High risk APL (WBC > 10 x 10⁹/L) – APML4 Protocol**

The APML4 regimen consists of induction with ATRA, idarubicin, and ATO followed by 2 consolidations with ATRA and ATO without chemotherapy, and then maintenance with ATRA, oral methotrexate (MTX), and 6-mercaptopurine (6-MP). The schema is detailed below.

**Figure 2. Schema of High Risk APL (APML4) Protocol**
**Induction Regimen:**
- ATRA 45mg/m$^2$/day in 2 divided doses (rounded to the nearest 10 mg increment) on Days 1-36
- Idarubicin, age-adjusted (see Figure 2 above), IV on Days 2, 4, 6, and 8
- ATO 0.15 mg/kg/day IV over 2 hours daily on Days 9-36
- Prednisone 1 mg/kg/day (rounded to nearest 5 mg) po for at least 10 days or until WBC < 1 x 10$^9$/L (administered prophylactically to all patients regardless of WBC count at presentation) or until resolution of differentiation syndrome (whichever occurs last)

**Consolidation Regimen (Cycles 1 & 2):**
- ATRA 45mg/m$^2$/day in 2 divided doses (rounded to the nearest 10 mg increment) on Days 1-28
- ATO 0.15 mg/kg/day IV over 2 hours daily on Days 1-28

Consolidation cycle 2 was administered 3-4 weeks after the completion of consolidation cycle 1. Please note that in the APML4 protocol, ATRA and ATO were administered intermittently in cycle 2 (to facilitate outpatient administration of ATO and to minimize the risk of developing ATRA resistance).

**Maintenance:**
Maintenance therapy started 3-4 weeks after the completion of consolidation cycle 2 and continued for 2 years. Maintenance therapy consists of eight 3-monthly cycles.

- ATRA 45mg/m$^2$/day in 2 divided doses (rounded to the nearest 10 mg increment) on Days 1-14. ATRA was administered alone for the first 2 weeks of each cycle.
- oral MTX 5-15 mg/m$^2$/week on Days 15-90
- oral 6-MP 50-90 mg/m$^2$/day on Days 15-90

MTX and 6-MP dosing was aimed at targeting an ANC of 1-2 x 10$^9$/L with dose adjustments for excessive myelosuppression or hepatotoxicity.

**Supportive Care:**
See 6.2.1.1 above.

**6.2.1.3 Other Chemotherapy Regimens (if contraindications to arsenic) – Low-intermediate and High risk APL**
Start ATRA on Day 1 of induction, daunorubicin on Day 6. For patients with high white blood counts (WBC > 10 x 10$^9$/L) and evidence of leukostasis, begin daunorubicin immediately on Day 1.

Since ATRA is only available as 10 mg caplets, doses should be multiples of 10 mg. All doses should be taken with meals in 2 divided doses (i.e. breakfast and dinner).
Because patients presenting with high WBC have a higher relapse rate, combined maintenance therapy is given these patients using 6-MP, methotrexate and ATRA. Low white count APL patients receive ATRA alone for maintenance.

**Inclusion Criteria:**
- APL ≤ age 60 (all patients regardless of WBC)
- APL > age 60 presenting with WBC > 10 x 10^9/L
- For patients > age 60 presenting with WBC < 10 x 10^9/L, delete ara-C from induction and consolidation

**Induction Regimen:**
- all-trans retinoic acid (ATRA) 45 mg/m^2/day in 2 divided doses for 28 days.
- daunorubicin 60 mg/m^2/day IV on Days 6, 7, 8. Start on Day 1 if WBC ≥ 10 x 10^9/L
- cytarabine 100 mg/m^2/day continuous IV infusion x 7 days on Days 1-7

If WBC begins rising or signs of ATRA syndrome develop prior to Day 6, begin daunorubicin and cytarabine immediately. If signs of ATRA (APL) syndrome or if WBC ≥ 10 x10^9/L, begin Dexamethasone 10 mg IV BID x at least 3 days.

**Consolidation Regimen Cycle 1:**
- ATRA 45mg/m^2/day in 2 divided doses x 28 days
- daunorubicin 60 mg/m^2/day on Days 1, 2, 3
- cytarabine 100 mg/m^2/day continuous IV infusion x 7 days on Days 1-7

**Consolidation Regimen Cycle 2:**
(N.B. MUGA scan prior to starting cycle 2)
- ATRA 45mg/m^2/day in 2 divided doses x 28 days
- daunorubicin 45mg/m^2/day on Days 1, 2, 3
- cytarabine 1.5 g/m^2 q12h x 6 doses on Days 1, 3 and 5

Indomethacin 25 mg po tid, or celecoxib 100 mg po bid, for five days with high dose cytarabine. Predforte eye drops qid x 7 days with high-dose cytarabine.

Consolidation may be given as an inpatient or outpatient. For outpatient therapy patients will be seen daily in transfusion unit for evaluation and hydration. For consolidation #2, the 1, 3 and 5 doses of ara-C will be given in the transfusion unit, while the 2, 4 and 6 doses will be given at home by AIP.
APL Consolidation Regimen
Newly Diagnosed
Age up to 60 years

Hydration
(Normal Saline)

Consolidation Chemotherapy Cycle 1

LVEF 50% or greater
Trastuzumab 6mg/kg every 3 weeks x 3

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

LVEF 40-49% or decreased > 10% from baseline
Amantadine 30 mg twice daily x 5 days on D1-5

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

Hydration
(Normal Saline)

Consolidation Chemotherapy Cycle 2

LVEF 50% or greater
Trastuzumab 6mg/kg every 3 weeks x 3

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

LVEF 40-49% or decreased > 10% from baseline
Amantadine 30 mg twice daily x 5 days on D1-5

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

Other Supportive Measures
Granisetron 1 mg IV daily x 3-5 days

Indomethacin 25 mg po bid or Celebrex 100 mg po bid x 5 days (to prevent cytarabine-induced fevers)

Prednisone eye drops qid x 7 days (to prevent cytarabine-induced conjunctivitis)

Ciprofloxacin 500 mg po bid and Amoxicillin 500 mg po bid from Day 8 onwards (stop if IV antibiotics initiated)

MUGA scan prior to each consolidation

APL Consolidation Regimen
Newly Diagnosed
Age over 60 years

Hydration
(Normal Saline)

Baseline WBC < 10 x 10^9/L

Consolidation Chemotherapy Cycle 1

LVEF 50% or greater
Trastuzumab 6mg/kg every 3 weeks x 3

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

LVEF 40-49% or decreased > 10% from baseline
Amantadine 30 mg twice daily x 5 days on D1-5

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

Baseline WBC > 10 x 10^9/L

Consolidation Chemotherapy Cycle 2

LVEF 50% or greater
Trastuzumab 6mg/kg every 3 weeks x 3

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

LVEF 40-49% or decreased > 10% from baseline
Amantadine 30 mg twice daily x 5 days on D1-5

ATRA 45 mg/m² on days 1-3

Cytarabine 150 mg/m² on days 1, 3, 5

Baseline WBC > 10 x 10^9/L

Other Supportive Measures
Granisetron 1 mg IV daily x 3-5 days

Indomethacin 25 mg po bid or Celebrex 100 mg po bid x 5 days (to prevent cytarabine-induced fevers)

Prednisone eye drops qid x 7 days (to prevent cytarabine-induced conjunctivitis)

Ciprofloxacin 500 mg po bid and Amoxicillin 500 mg po bid from Day 8 onwards (stop if IV antibiotics initiated)

MUGA scan prior to each consolidation

Last Revision Date – August 19, 2019
6.2.2 Recurrent/Persistent Disease
Chemotherapy with ATRA, daunorubicin and cytarabine is used to treat persistent disease (see 6.2.1.3 above). Recurrent disease can be treated with an ATRA and ATO based regimen or chemotherapy (see 6.2 above).

6.3 Radiation Therapy
Radiation therapy is not used routinely in APL treatment. Radiotherapy plays a role in the control of CNS leukemia, the control of resistant localized disease (e.g. persistent paraspinal mass), and in pre-transplant conditioning.

6.4 Other Therapy
6.4.1 Coagulopathy and Thrombosis
APL is very frequently associated with both a coagulopathy and with thrombotic events, or both.

The former is treated with “round-the-clock” ongoing assessment of coagulation status coupled with vigorous, ongoing replacement with frozen plasma, platelets, and cryoprecipitate, fibrinogen concentrate (Riastap®) etc., with the goal of maximally correcting the INR and keeping the fibrinogen > 1 g/L. Antifibrinolytic agents such as tranexamic acid should NOT be used routinely. ATRA must be started promptly at the first suspicion of APL.

Thrombotic events are particularly problematic, as it is often associated with a coagulopathy as well. Vigorous factor and platelet replacement should proceed as above. Patients can be anticoagulated with low dose heparin (50-100 units per hour) in preparation for insertion of a removable SVC filter (stop heparin 1 hour before insertion).
After umbrella insertion, with ongoing correction of coagulopathy, anticoagulation can proceed at “low dose” levels of unfractionated heparin (or at ~75% dose of LMWH) as long as platelets are > 20-30 x 10^9/L, and coagulopathy is corrected. ATRA must be started promptly at the first suspicion of APL.

6.4.2 Ongoing MRD Monitoring
APL leukemic burden can be assessed by PCR, at least in cases carrying the classical t(15;17) translocation (others can also be monitored by PCR, although this capability is not generally available; they can be monitored by FISH (which is less sensitive, however).

After count recovery following ATRA and ATO based-induction therapy, a significant proportion of patients remain PCR positive (i.e. ~30% treated on the APML4 protocol; not specified in the low-intermediate risk LoCoco protocol) although their marrows are in morphological CR. However, the presence of measurable cytogenetic or PML-RARα levels does not have prognostic or therapeutic implications at this time point.

After the completion of the second or third consolidation in the ATRA and ATO based-regimens (i.e. high-risk APML4 protocol and low-intermediate risk LoCoco protocol, respectively), over 95+% of patients have become PCR negative. Those rare patients who remain PCR positive after completion of consolidation therapy (with the low-intermediate risk LoCoco and high risk APML4 protocols) require further treatment for persistent disease (see 6.2.2 above).

APL patients are seen every three months for two years, then every 6 months for 1-2 years, and yearly thereafter. In addition to careful review of bloodwork and clinical status, molecular analyses are performed routinely for the first 3-4 years. Prior practice guidelines in the era of ATRA and chemotherapy (i.e. prior to ATRA and ATO based regimens) have recommended PML-RARα PCR monitoring every 3 months for 2-3 years then every 6 months for 1 year, as early intervention in patients with evidence of MRD yields better outcomes than when treated in morphological relapse. However, clinical experience indicates that the risk of relapse for patients with low-intermediate risk APL treated with the low-intermediate risk LoCoco protocol is low, therefore, the utility of performing serial marrows to assess for measurable residual disease in this group of patients is unclear and not be necessary. Changes in PCR status are confirmed by prompt repeat testing. Patients who convert from PCR negative to PCR positive status should be treated for recurrent disease (see 6.2.2 above) without waiting for overt hematological relapse (which will occur in >90% of such cases within one year).

6.4.3 Autologous and allogeneic stem cell transplantation (SCT).
There currently is no role for autologous or allogeneic stem cell transplant (SCT) in molecularly negative APL in CR1.

However, SCT becomes an option in APL patients with persistent or recurrent disease (see 6.2.2 and 6.4.2 above).
Patients with persistent or recurrent disease, who with further treatment achieve CR and become molecularly negative, should proceed to autologous SCT (autoSCT). This is currently the only indication for autoSCT in AML at Princess Margaret Cancer Centre.

Patients with persistent or recurrent disease, who with further treatment achieve CR but remain molecularly positive, should proceed to allogeneic SCT (alloSCT).

6.5 Oncology Nursing

Refer to general oncology nursing practice

7. Supportive Care

7.1 Patient Education

APL patients and their families receive extensive education (by physicians and specialty nurses) at the time of diagnosis. This education is then reviewed and reinforced during their inpatient and outpatient treatment. Additional teaching occurs prior to and at the time of initial discharge, and this teaching is reviewed during outpatient follow up.

An extensive patient education package which covers all aspects of their care has been prepared for this patient group.

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to general oncology palliative care guidelines

8. Follow-up Care

APL patients that proceed to alloSCT are followed by the alloSCT service. APL patients that proceed to autoSCT are shortly returned to the leukemia service for follow-up.
AML patients that do not proceed to alloSCT are supervised closely by the leukemia service during the completion of their induction and consolidation chemotherapy, and are then followed on an ongoing basis. Specifically, patients are seen every three months for two years, then every 6 months for 1-2 years, and yearly thereafter. In addition to careful review of bloodwork and clinical status, molecular analyses are performed routinely for the first 3-4 years. Prior practice guidelines in the era of ATRA and chemotherapy (i.e. prior to ATRA and ATO based regimens) have recommended PML-RARα PCR monitoring every 3 months for 2-3 years then every 6 months for 1 year, as early intervention in patients with evidence of MRD yields better outcomes than when treated in morphological relapse. However, clinical experience indicates that the risk of relapse for patients with low-intermediate risk APL treated with the low-intermediate risk LoCoco protocol is low, therefore, the utility of performing serial marrows to assess for measurable residual disease in this group of patients is unclear and not be necessary. Changes in PCR status are confirmed by prompt repeat testing. Patients who convert from PCR negative to PCR positive status should be treated for recurrent disease (see 6.2.2 above) without waiting for overt hematological relapse (which will occur in >90% of such cases within one year).
References