PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

LEUKEMIA

ACUTE PROMYELOCYTIC LEUKEMIA
Leukemia Site Group – Acute Promyelocytic Leukemia

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1. **Introduction**
These guidelines relate to the management of APL as currently practiced at Princess Margaret Hospital. While a subtype of 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 **FAB classification** (1976, 1985, 1991), and features distinctive morphology:

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Cytochemistry</th>
<th>Immunophenotype</th>
<th>Cytogenetics</th>
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<tbody>
<tr>
<td>M0 Myeloblastic, with no differentiation</td>
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<tr>
<td>M1 AML, minimal myeloid maturation</td>
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<td>M2 AML, with maturation</td>
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<tr>
<td>M3 Promyelocytic</td>
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M4 Myelomonocytic
M5 Monocytic
M6 Erythroleukemia
M7 Megakaryoblastic

In the more recent **WHO classification** (2002, 2009), APL falls into the category AML with characteristic genetic abnormalities:

- AML with characteristic genetic abnormalities
  - t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(6;9), inv(3) or t(3;3), t(1;22)
- AML with myelodysplasia related changes
- AML with prior MDS or MPD
- AML, therapy-related
- AML with prior chemotherapy and/or radiation
  - -5, -7, 11q23
- AML not otherwise categorized
  - AML not falling into the above categories
- Acute leukemias of ambiguous lineage
  - Mixed lineage or biphenotypic acute leukemia

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

APL-related translocations can be detected by karyotypic analysis, and also by FISH analysis using an \textit{RAR}\textsubscript{\alpha} • break-apart probe.

\textbf{5iii. Molecular}

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

While, the \textit{RAR}\textsubscript{\alpha} • breakpoint always lies within intron 2, the \textit{PML} breakpoint can lie in intron 3 (BCR3; S form), intron 6 (BCR1; L form) and exon 6 (BCR2; V form).

Such molecular testing, as appropriate, also plays an important role in ongoing, post-remission, APL minimal residual disease (MRD) assessment (see 6. and 8. below). Specifically, after counts recovery following induction chemotherapy, the majority (~95%) of patients remain PCR +ve although their marrows are in morphological CR. After the completion of the second consolidation, however, ~95% of patients have become PCR -ve. Those few who remain PCR +ve 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-ve to PCR+ve 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, an appropriate individualized treatment plan is chosen. Due to its high curability, APL is usually treated aggressively, even in very elderly patients.

^APL - Prognostic factors
  t(15;17) confers good risk
  t(11;17) confers poor risk due to ATRA and arsenic resistance
  Lkc > or < 10 bil/L
  Platelet count < 40 bil/L
  CD56+
  PML breakpoint; BCR2 and 3 may confer worse outcome

Chemotherapy protocols for newly diagnosed APL patients are listed in 6.2 below.

Chemotherapeutic 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 Chemotherapy
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.
Treatment is defined primarily by presentation Lkc, and patient age:

Disease: ACUTE PROMYELOCYTIC LEUKEMIA

Code: 0701APL1 (induction) 0702APL2 (consolidation) 0007AML10,11 (maintenance) (Updated Sept 2010).

Background Information:
APL has its own chemo regimen, using ATRA and daunorubicin without cytarabine during induction. Cytarabine is introduced during consolidation. Start ATRA on day 1 of induction, daunorubicin on day 6. For patients with high white blood counts (WBC>10x109/L) and evidence of leukostasis, begin daunorubicin immediately on day
1.

Since ATRA is only available as 10mg caplets, doses should be multiples of 10mg. 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)
• APL > age 60 presenting with WBC > 10 x 10⁹/L
• For pts. > age 60 presenting with WBC < 10, delete ara-C from induction and consolidation.

INDUCTION REGIMEN
• all-trans-retinoic acid (ATRA) 45mg/m₂/day in 2 divided doses for 28 days.
• daunorubicin 60mg/m²/day IV, on Days 6, 7, 8. Start on Day 1 if WBC > 10x10⁹/L.
• cytarabine 100 mg/m²/day continuous IV infusion x 7 days, 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 > 10x10⁹/L, begin Dexamethasone 10 mg IV BID x at least 3 days.

CONSOLIDATION REGIMEN CYCLE #1
• ATRA 45mg/m₂/day in 2 divided doses x 28 days
• daunorubicin 60 mg/m₂/day on Days 1, 2, 3
• cytarabine 100 mg/m₂/day continuous IV infusion x 7 days, Days 1-7

CONSOLIDATION REGIMEN CYCLE #2
(N.B. MUGA scan prior to starting cycle 2)
• ATRA 45mg/m₂/day in 2 divided doses x 28 days
• daunorubicin 45mg/m₂/day on Days 1, 2, 3
• cytarabine 1.5 g/m q12h x 6 doses, Days 1, 3 and 5

Indomethacin 25 mg po tid, or celcoxib 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.
6.2.2 Recurrent/Persistent Disease

Disease: ACUTE PROMYELOCYTIC LEUKEMIA
Status: Recurrent/Persistent Disease
Age up to 60 years and over 60 years
Eponym: 
Code: 9

PATIENT ELIGIBILITY:
1. Molecular or morphologic recurrence, or failure to become molecularly –ve after the completion of two consolidations.

REINDUCTION/PERSISTENT DISEASE REGIMEN
• Arsenic trioxide (ATO) 0.15 mg/kg/day IV daily x 30 days (D 1-30)
• ATRA 25 mg/m^2/day po in 2 divided doses x 28 days (D 1-28)

CONSOLIDATION REGIMEN
• Same as 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 (eg. 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 etc., with the goal of maximally correcting the INR and keeping the fibrinogen >1. Antifibrinolytic agents such as tranexamic acid should NOT be used routinely. ATRA must be started promptly at the first suspicion of APL.

The latter is 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 bil/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). 10

Specifically, after counts recovery following induction chemotherapy, the majority (~95%) of patients remain PCR +ve although their marrows are in morphological CR.

After the completion of the second consolidation, however, ~95% of patients have become PCR -ve. Those few who remain PCR +ve at this point 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. Changes in PCR status are confirmed by prompt repeat testing. Patients who convert from PCR-ve to PCR+ve 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 auto- or alloSCT in molecularly -ve 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 -ve, should proceed to autoSCT. This is currently the only indication for autoSCT in AML at PMH.

Patients with persistent or recurrent disease, who with further treatment achieve CR but remain molecularly +ve, should proceed to 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.