

Acute Promyelocytic Leukemia

Effective Date: October 2025



Background

Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia (AML), characterized by abnormal promyelocytes and a translocation involving chromosomes 15 and 17 leading to a PML-RARa fusion gene product. APL accounts for 5-10% of all AML diagnosed with an incidence in Canada of 0.083/100 000 (1-2). The median age is 30 with a male to female ratio of 1:1. After age 20 the age-specific incidence is constant until a decline at age 60-70[Type a quote from the document or the summary of an interesting point. You can position the text box anywhere in the document. Use the Drawing Tools tab to change the formatting of the pull quote text box.]

(1,3). Therapy-related APL has been reported after chemotherapy and radiation exposure, particularly after topoisomerase II inhibitors in patients treated for breast cancer (1).

The prognosis of APL is excellent, with a complete remission rate greater than 90% and a 5-year overall survival of 80-90%. The reported risk of early mortality is 10%, primarily due to hemorrhage, sepsis or differentiation syndrome. Recent data from a Canadian cancer registry estimated a higher rate of early mortality in APL of 22% (10.6% in <50 years old, 35.5% in >50 years old) (2,4,5).

APL has distinct clinical features and management when compared to other forms of AML. This document serves as a supplement to the AML guidelines, to specifically address the differences in the diagnosis and management of APL.

Guideline Questions

- What are the diagnostic criteria for APL?
- What is the recommended management for adult patients in Alberta with APL?
- What is the recommended follow-up for adult patients in Alberta with APL?

Search Strategy

The MEDLINE (1996 to March 2015), ASCO abstracts and proceedings, and ASH abstracts and proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and clinical trials. For the 2023 update, the evidence was reviewed and no major content changes were made.

Target Population

The following guidelines apply to adults over the age of 18 years only.

Recommendations

Diagnosis and Prognosis

1. Urgent testing for the translocation (15;17) and/or gene product (PML-RARa) must be done by karyotype, fluorescence *in situ* hybridization (FISH) and/or molecular testing to confirm the diagnosis of acute promyelocytic leukemia (APL).

2. The prognosis of APL is excellent, with further risk stratification based on the WBC and platelet count (Sanz risk score).

Management

3. Supportive management includes aggressive monitoring and treatment of coagulopathy, differentiation syndrome, as well as preventing prolonged QTc and arrhythmias on arsenic trioxide (ATO) therapy.
4. For low-intermediate risk patients (WBC ≤ 10.0), the Lo-Coco protocol (ATRA and ATO alone) is recommended.
5. For high-risk patients (WBC > 10), the addition of an anthracycline to induction, based on the APML4 protocol or the APOLLO protocol, is recommended. If anthracyclines are contraindicated, cytarabine may be substituted.
6. The recommended ATO dose is 0.15 mg/kg/day, capping the dose at 10 mg daily. Temporary dose interruption or reduction may be needed for liver toxicity or QTc prolongation.

Follow-up in Low-Intermediate Risk Patients (WBC ≤ 10.0)

7. A bone marrow examination to assess complete remission should be done after induction in the Lo-Coco protocol, to document hematologic CR. Molecular remission must be documented by the end of the final cycle of consolidation.
8. Molecular monitoring by PCR is not recommended in low-intermediate risk patients given the very low risk of recurrence in this population.

Follow-up in High Risk Patients (WBC > 10)

9. A bone marrow examination to assess complete remission should be done after either induction or the first cycle of consolidation is completed, to document hematological CR. Molecular remission must be documented by the end of the final cycle of consolidation.
10. Sequential molecular monitoring by peripheral blood PCR is recommended in high-risk patients every 3 months for a total of 36 months post-consolidation, to detect molecular relapse and guide pre-emptive therapy.

Discussion

Diagnosis

While the peripheral blood and bone marrow specimen are helpful in identifying the possibility of APL, urgent testing for the pathognomonic translocation (15;17)(q22;q21) and/or gene product (PML-RARa) must be done by karyotype, fluorescence *in situ* hybridization (FISH) and/or molecular testing to confirm the diagnosis. The 2008 WHO Classification characterizes APL under ‘acute myeloid leukemia with recurrent genetic abnormalities’, no blast count cutoff is required once the cytogenetic abnormality is confirmed (6). The characteristic flow cytometry immunophenotype is CD13+ CD33+ CD34- CD117+ CD56- CD15- CD11b- HLA DR- (6).

Rare complex cryptic translocations producing the PML-RARa gene product are possible. Seven variant *RARA* translocations exist in less than 5% of cases and include: *NPM1*, t(5;17); *NUMA1*,

t(11;17); *ZBTB16/PLZF, t(11;17); *STAT5B, t(17;17), PRKAR1A, t(17;17); FIP1L1, t(4;17); and IRF2BP2, t(1;17) (6-8).

*Variants with reported resistance to all-*trans*-retinoic acid (ATRA).

The molecular abnormality *FLT3* ITD is seen in 12-40% of APL cases, and is associated with leukocytosis, the short PML/RARA (BCR3) isoform and microgranular morphology (9-10).

A prominent presenting feature of APL is disseminated intravascular coagulopathy (DIC) leading to hemorrhagic symptoms and occasionally thrombosis (11). Patients may have evidence of soft tissue infiltration (skin, gingiva). Unlike other forms of AML, the total white blood cell count is low or normal. In contrast to typical APL, the microgranular variant of APL is associated with significant leukocytosis with a rapid doubling time.

Investigations

Please see AML guidelines for appropriate investigations. In APL this includes regular monitoring for DIC (CBC, INR/PT, PTT, fibrinogen), and a baseline EKG to assess the QTc interval. Cardiac function should be assessed by means of an echocardiogram or nuclear medicine scan.

Prognosis

Based on a multivariate regression analysis of relapse-free survival from PETHEMA and GIMEMA studies using ATRA+chemotherapy regimes, Sanz et al. identified the initial WBC and platelet count as independent prognostic factors and created a simple risk score that is widely used (12):

Sanz Risk Category		3-year Relapse-free Survival
Low Risk	WBC count ≤ 10.0, platelet count > 40 x 10 ⁹ /L	98%
Intermediate Risk	WBC count ≤ 10.0, platelet count ≤ 40 x 10 ⁹ /L	89%
High Risk	WBC count > 10 x 10 ⁹ /L	70%

Early severe differentiation syndrome (DS) is associated with mechanical ventilation and a higher rate of death during induction therapy (40% versus 7%) (13). Risk factors for developing DS are an elevated WBC (>5 x 10⁹/L) and abnormal renal function (13). Other predictors for early mortality secondary to differentiation syndrome include ECOG ≥2 and low albumin (5). Severe DS has also been associated with the development and death relating to hemorrhage (13-14). Risk factors for early mortality secondary to hemorrhage include WBC >10, peripheral blast count >30, abnormal renal function, and presence of coagulopathy (5).

Other poor prognostic factors include post-therapy MRD positivity and age (15). *FLT3* ITD may be associated with a poor prognosis, however, this has not been consistent in all studies and recent

studies evaluating upfront arsenic trioxide therapy show no difference in outcome based on *FLT3* status (9,10,16,17). Unlike other subtypes of AML, there is no prognostic difference in therapy-related APL (1).

Treatment

Initial Management

Once the diagnosis of APL is suspected, treatment with ATRA should be started as soon as possible at a dose of 45 mg/m²/day (rounded to the nearest 10 mg) divided into twice daily dosing, to initiate differentiation of leukemic promyelocytes and improve the coagulopathy and risk of hemorrhage. Appropriate counseling around ATRA's teratogenicity is recommended, including pregnancy testing in women of reproductive age, as appropriate (18).

Supportive Treatment

- 1) Procedures: To avoid hemorrhagic and thrombosis complications, consideration of a peripherally inserted central catheter (PICC) with multiple lumens is recommended instead of a central line. Lumbar punctures should be avoided. In the setting of leukocytosis, leukopheresis is not recommended given the risk of exacerbating a coagulopathy.
 - 2) Coagulopathy: Frequent lab monitoring (at a maximum interval of every 6 hours) and blood product support are needed when there is evidence of coagulopathy. Transfusions are recommended to keep a platelet count >30 x 10⁹/L, fibrinogen level >1.5 g/L, and a normal INR/PT. Heparin is not recommended unless there is evidence of venous thromboembolism. Standard transfusion recommendations apply when there is no further evidence of coagulopathy.
 - 3) Differentiation Syndrome: Differentiation syndrome (DS) can be caused by ATRA or arsenic trioxide (ATO) and is suspected with the presence of one of the following: unexplained fever, weight gain >5 kg, peripheral edema, dyspnea with pulmonary infiltrates on chest radiograph, unexplained hypotension, acute renal failure, or pleuropericardial effusion (18-19). These symptoms and signs are non-specific and other diagnoses such as pneumonia, sepsis, cardiac toxicity and pulmonary hemorrhage should also be considered. Severe DS is defined as 4 or more of the above signs or symptoms, and moderate DS is defined as 2-3 of the above signs or symptoms (13). The incidence of DS has a bimodal peak in the first and third week in both moderate and severe DS, with severe DS occurring earlier (median 6 days) compared to moderate DS (median 15 days) (13).
- The use of prophylactic steroids in DS is controversial, with little evidence to guide therapy (20). Steroids are routinely given as part of the protocols using upfront ATO therapy, at prednisone 0.5-1.0 mg/kg per day starting on Day 1 for part or all of induction therapy. (17,21).
- If differentiation syndrome is suspected, increasing steroids to therapeutic doses (dexamethasone 10 mg IV Q12H) is recommended. Consider holding ATRA and ATO in cases of severe differentiation

syndrome. Other supportive measures include furosemide and less commonly hemodialysis or mechanical ventilation. The patient should be in a monitored setting, early involvement of the intensive care team is recommended for progressive and/or severe DS (18,20).

4) Use of cytoreductive therapy: Use of a chemo-free regimen such as the Lo-Coco protocol is frequently associated with hyperleukocytosis during induction, which may increase the risk of DS. Hydroxyurea should be used to control the WBC count (500 mg QID if WBC 10-50 x 10⁹/L or 1 gram QID if WBC >50 x 10⁹/L. Pre-emptive use of hydroxyurea if WBC <10 x 10⁹/L may be warranted in the setting of a rising WBC). If ineffective, cytarabine 100-200 mg IV may also be used to control the WBC.

5) Arrhythmias on Arsenic Trioxide: Baseline and regular EKGs are recommended while on ATO therapy to monitor the QTc (a minimum of EKGs 2x/week). Other QT-prolonging medications should be avoided if possible. Replacement of potassium and magnesium should be done to keep electrolyte levels in the upper limit of normal (K>4, Mg>0.75) while a patient is on ATO. ATO should be temporarily held if there is evidence of an arrhythmia, or until low electrolytes are replaced and the QTc has normalized.

6) Liver toxicity on ATO: Use of ATO is frequently associated with transient liver enzyme elevations, particularly during induction therapy. If AST/ALT rises to >5x ULN, the ATO may need to be temporarily interrupted, or the dose reduced.

6) Antibiotic prophylaxis: Because cases of HSV and VZV reactivation have been observed, anti-viral prophylaxis (e.g. valacyclovir) is advisable. Invasive fungal infections appear to be less common in APL than in AML but can occur (49). Although the above studies with ATO + ATRA did not report on the use of anti-fungal prophylaxis, its use can be considered, given the expected duration of neutropenia. However, azoles should be avoided due to QTc prolongation and potential drug interactions with ATRA. For patients receiving prolonged courses of corticosteroid prophylaxis, PJP prophylaxis with co-trimoxazole should also be considered.

7) Tumor lysis syndrome: Monitor for tumor lysis syndrome, with allopurinol for patients at high risk of tumor lysis syndrome.

8) Nutritional support: A daily multivitamin is recommended to prevent thiamine deficiency, particularly if patients have other risk factors for malnutrition. Neurological symptoms are common in ATO, with case reports of thiamine deficiency described in patients with APL on ATO therapy (21).

APL Therapy

Background

The introduction of the retinoid ATRA has improved disease free survival and overall survival in APL, and has become the backbone of APL treatment (16, 23-27). When used concurrently with induction, consolidation and maintenance chemotherapy, ATRA decreases disease relapse, with the added risk of differentiation syndrome up to 25% (13,16,25,27,28,29).

Compared to other subtypes of acute myeloid leukemia, APL has shown increased sensitivity to anthracycline chemotherapy. Prior to the ATRA era, anthracycline monotherapy was shown to have superior event-free survival with similar complete remission rates and overall survival, when compared to a standard “3 + 7” regime (30). The role of cytarabine continues to be evaluated in high-risk patients (WBC >10) (31-32).

Arsenic trioxide induces differentiation and apoptosis of APL cells. ATO binds to the PML portion of the PML-RARA fusion protein, and ATRA binds to the RARA moiety, synergistically inducing PML-RARA protein degradation via independent pathways (33-35). Recent studies show improved clinical outcomes with the combination of ATRA and ATO in the upfront treatment of APL (17, 21, 36-41). The use of ATRA+ATO is also cost-effective in Canada when compared to ATRA+chemotherapy (42). Risks of ATO include differentiation syndrome, neurological side effects, liver enzyme elevation and arrhythmias.

Several studies have incorporated patients' white cell counts as a risk factor in treatment protocols, either excluding patients or escalating chemotherapy regimes when the initial WBC is greater than 10. (17,21,24,25,31,40). Studies have also evaluated risk-adapted therapy, with de-escalation of therapy for patients with low-intermediate risk disease (31). Of the clinical trials evaluating ATO in the upfront setting, omitting standard chemotherapy like idarubicin has only been evaluated in a low-intermediate risk population with WBC ≤10.0. (17,21,36,39).

Upfront setting

Low-intermediate risk group: We recommend treatment with a combination of ATRA+ATO for induction and consolidation therapy based on the protocol published by the Lo-Coco et al. (21). The use of ATRA+ATO was at least non-inferior to ATRA+Idarubicin at 2 years, with less cytopenias and infectious complications (21). The ATRA+ATO arm had more hepatotoxicity, prolonged QTc and leukocytosis, however there was no difference in the rate of differentiation syndrome between arms (21).

As per the Lo-Coco protocol, ATRA+ATO should be continued in induction until hematologic CR, or a maximum of 60 days. This should be followed by 4 consolidation cycles of ATRA+ATO.

High-risk group: The addition of an anthracycline to ATRA and ATO during induction is recommended in patients with high-risk disease, based on the initial WBC count >10 x 10⁹/L. There are 2 regimens which have reported favourable results. The APML4 protocol (17,36) consists of induction with Idarubicin x4 doses + ATRA + ATO, followed by two consolidation cycles of ATRA+ATO, followed by 2 years of maintenance therapy with ATRA, 6MP and methotrexate. More recently, the APOLLO study utilized 2 doses of idarubicin + ATRA + ATO in induction, followed by 4 cycles of consolidation with ATRA + ATO and no maintenance therapy. In this study the 2-year event-free survival was 89%, which was superior to the control arm that received chemotherapy + ATRA (50).

In patient for whom anthracycline therapy is contraindicated (e.g. impaired left ventricular function or poor liver function), cytarabine may be used instead of idarubicin, based on anecdotal experience.

Although the ATO dose in these studies was set at 0.15 mg/kg/day, a recent study reported that capping the ATO dose at 10 mg/day was associated with a lower incidence of neurotoxicity during consolidation therapy, and had comparable efficacy (51).

In all of these upfront ATO protocols, CNS prophylaxis is not recommended. Neurological testing (lumbar puncture and/or MRI) should only be performed if there are symptoms or signs suggestive of neurological involvement.

In addition to usual AML treatment, patients should be monitored for rash, differentiation syndrome, coagulopathy, prolonged QTc/arrhythmias and elevated liver enzymes.

Lo-Coco protocol (n=77 in ATRA+ATO arm)	2-year outcomes
Cumulative incidence of relapse	1%
Event-free survival	97%
Disease-free survival	97%
Overall survival	99%
APML4 protocol (n=124; 24 high risk)	
Cumulative incidence of relapse	2.5%
Failure-free survival	88.1%
Disease-free survival	88.1%
Overall survival	93.2%
APOLLO protocol (n=68, all high risk)	
Cumulative incidence of relapse	0%
Event-free survival	89%
Overall survival	93%

Elderly patients

A chemotherapy-free regime using ATO+ATRA is recommended in low-intermediate elderly patients, to minimize toxicity. In the phase 3 trial published by Lo-Coco et al, there were 35 patients enrolled between the ages of 60-70. The 2-year event-free survival rates were 100% in the ATRA+ATO group, compared to 84% in the ATRA+Idarubicin group (4 deaths from differentiation syndrome, pulmonary embolism and bronchopneumonia). (43). The APML4 or APOLLO protocol is recommended in high-risk elderly patients, substituting cytarabine for idarubicin if the latter is contraindicated, as described above..

Relapsed setting

We recommend ATO therapy in the relapsed setting for an ATO-naïve patient (45). In transplant-eligible patients, transplant is recommended to consolidate a remission after ATO, with the option of autologous transplantation in a patient without high-risk features who achieves a molecular remission with ATO therapy (45-47). Allogeneic transplant should be considered in all patients who do not achieve a molecular remission in second complete remission (CR2).

There is little evidence to guide recommendations in the setting of relapse after upfront ATO therapy. Arsenic-resistance has been reported, with presence of mutations in the PML-RARA B2 binding domain. Reinduction with ATRA+ATO should be used for late relapses. For early relapses, options include ATO, “3 + 7”, or other AML salvage regimes prior to transplant.

Follow-up

The timing of a follow-up bone marrow aspirate differs based on the protocol used. In the Lo-Coco protocol, a bone marrow aspirate is recommended after completion of induction treatment to document hematologic remission. In the APML4 protocol, a bone marrow aspirate is recommended after the first cycle of consolidation to document hematological remission, as the response may be delayed. The median time to hematological CR in the APML4 protocol was 53 days.

Molecular remission by PCR must be documented by the end of the final cycle of consolidation therapy, regardless of the protocol used.

Sequential monitoring for minimal residual disease (MRD) is only recommended in high risk patients to predict relapse and guide pre-emptive therapy (15, 48). In high risk patients, MRD testing is recommended every 3 months for 36 months post-consolidation therapy by the best possible PCR test available. MRD monitoring by peripheral blood specimen is recommended to minimize the risk of bone marrow procedures and increase adherence, however, MRD monitoring by peripheral blood does have decreased sensitivity with a delay in MRD positivity by a median of 29 days and a difference in 1.5 log reduction when compared to a bone marrow specimen (15). Post-consolidation molecular monitoring is not recommended in low-intermediate risk patients because of the very low risk of relapse using upfront ATRA + ATO therapy.

Future directions

Optimizing regimes with ATO are needed, including the logistics of administration and monitoring of ATO in an outpatient setting during consolidation. Oral arsenic therapy also needs to be explored further. Lastly, more evidence is needed in the relapsed/refractory setting with the shift to upfront ATRA + ATO therapy.

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Appendix A: Chemotherapy Regimens

Lo-Coco Protocol: ATRA+ATO

Induction:

ATO (Arsenic trioxide) (IV over 2 hours) 0.15 mg/kg/day (capped at 10 mg/day):

Starting on day 1, continued until hematological CR or maximum 60 days, see above guidelines for supportive measures

ATRA (All-trans retinoic acid) (orally) 45 mg/m²/day:

Starting on day 1, administered in two equally divided doses and rounded to the nearest 10mg increment, continued until hematological CR or maximum 60 days

Prednisone 0.5 mg/kg per day:

Starting on day 1 until the end of induction therapy

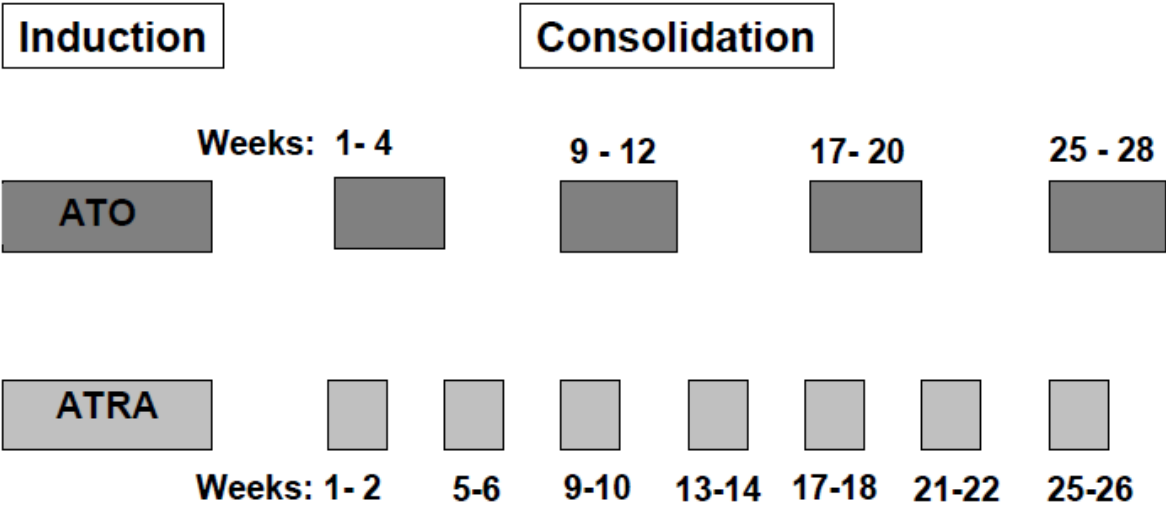
Consolidation:

ATO (IV over 2 hours) 0.15 mg/kg (capped at 10 mg) daily for 5 days every week

Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles (last cycle administered on weeks 25-28)

ATRA (orally) 45 mg/m²/day

Administered in two equally divided doses and rounded to the nearest 10 mg increment. Treatment should be administered for 2 weeks on and 2 weeks off for a total of 7 cycles (last cycle administered on weeks 25-26)



APML4 Protocol: ATRA+ATO+Chemotherapy

Induction:

ATRA (orally) 45 mg/m²/day:

Administered in two equally divided doses and rounded to the nearest 10 mg increment, on days 1-36

ATO (IV) 0.15 mg/m²/day:

Administered on days 9-36, see above guidelines for supportive measures

Idarubicin (IDA) (IV) 12 or 9 or 6 mg/m²/day based on age (18-60 years or 61-70 years or >70 years, respectively):

Administered on days 2, 4, 6, and 8

Prednisone 1 mg/kg/day:

Administered on days 1-10 or until WBC count falls below 1 x 10⁹/L or until resolution of differentiation syndrome (whichever occurs last)

When ATRA or ATO was omitted for 3 or more days, the treatment duration should be extended beyond day 36 to compensate for omitted doses

Consolidation:

Should begin 3-4 weeks after the end of induction.

First Consolidation cycle:

ATRA (orally) 45 mg/m²/day: Days 1-28

ATO (IV over 2 hours) 0.15 mg/kg/day: Days 1-28

Second Consolidation cycle:

ATRA (orally) 45 mg/m²/day: Days 1-7, 15-21, and 29-35

ATO (IV over 2 hours) 0.15 mg/kg/day: Days 1-5, 8-12, 15-19, 22-26, and 29-33

Maintenance: Eight 3-monthly cycles of:

ATRA (orally) 45 mg/m²/day: Days 1-14

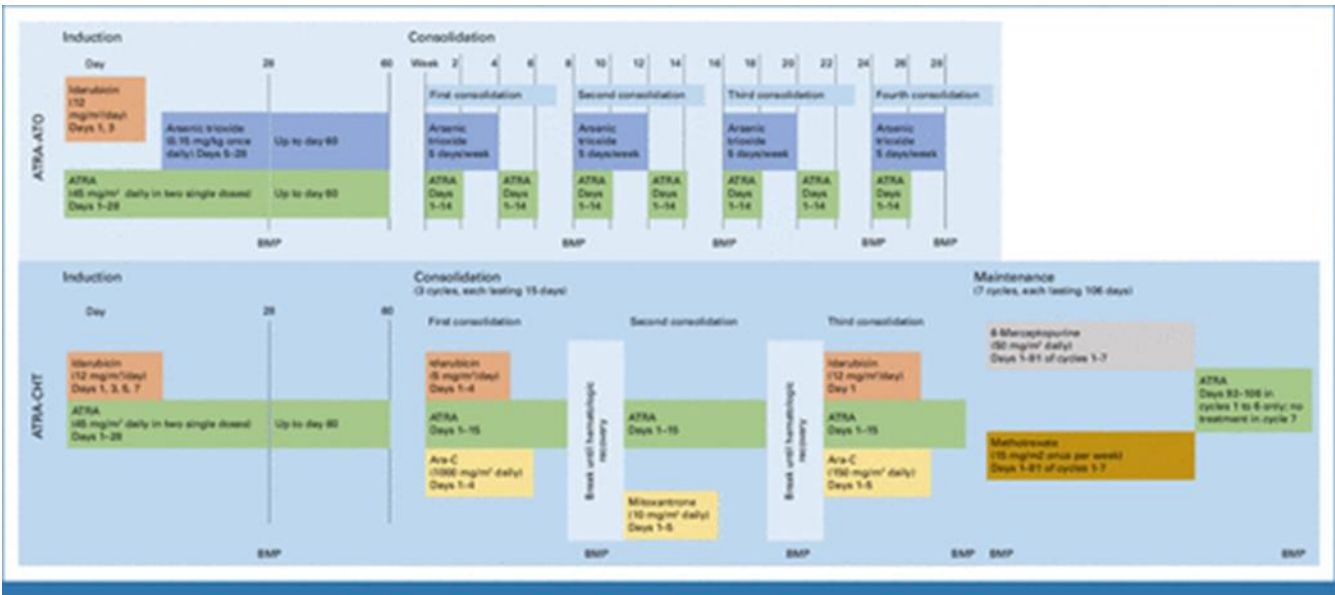
6-Mercaptopurine (6-MP) (orally) 50-90 mg/m²/day: Days 15-90

Methotrexate (MTX) (orally) 5-15 mg/m²/weekly: Days 15-90

APML4 Protocol

Induction		
ATRA	45 mg/m ² /d PO	Days 1-36 in divided doses
Idarubicin	12 mg/m ² /d IV (ages 1-60) 9 mg/m ² /d IV (ages 61-70) 6 mg/m ² /d IV (ages > 70)	Days 2, 4, 6, and 8
ATO	0.15 mg/kg/d IV	Days 9-36 as a 2-hour IV infusion Supplemental potassium and magnesium as required to maintain serum levels in the upper half of the respective normal ranges
Prednisone	1 mg/kg/d PO	Days 1-10 or until WBC count falls below 1×10^9 /L or until resolution of differentiation syndrome (whichever occurs last)
Hemostatic support	Products administered once or twice daily as required to achieve specified targets	Platelets $> 30 \times 10^9$ /L Normal prothrombin time Normal activated partial thromboplastin time Fibrinogen > 1.5 g/L
Consolidation cycle 1 (3-4 wks after the end of induction)		
ATRA	45 mg/m ² /d PO	Days 1-28
ATO	0.15 mg/kg/d IV	Days 1-28
Consolidation cycle 2 (3-4 wks after the end of consolidation cycle 1)		
ATRA	45 mg/m ² /d PO	Days 1-7, 15-21, 29-35
ATO	0.15 mg/kg/d IV	Days 1-5, 8-12, 15-19, 22-26, 29-33
Maintenance: 8 cycles (3-4 wks after the end of consolidation cycle 2)		
ATRA	45 mg/m ² /d PO	Days 1-14
MTX	5-15 mg/m ² /wk PO	Days 15-90
6MP	50-90 mg/m ² /d PO	Days 15-90

APOLLO Protocol



Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

The original guideline was developed in May 2015.

Maintenance

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2023. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

ATRA	All-trans-retinoic acid
ATO	Arsenic trioxide
CR	Complete remission
DS	Differentiation syndrome
MRD	Minimal residual disease

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).

Conflict of Interest Statements

***Dr. Joseph Brandwein** reports honoraria from Abbvie, Amgen, Astellas, BMS, Daiichi-Sankyo, Jazz, Paladin, Pfizer, and Servier.

Dr. Lynn Savoie has nothing to disclose.

Derek Tilley has nothing to disclose.

*Working group lead

Citation

Brandwein J (lead), Savoie L, Tilley D. Cancer Care Alberta, Alberta Health Services (2025). Clinical Practice Guideline on [APL, Version 3]. Accessed [Month, Year]. Available from: www.ahs.ca/guru