

Acute Myeloid Leukemia

Updated April 2008 by Dr. Richard Wells*

Updates: Minor changes including adjustment of therapy algorithms

Introduction

Acute myeloid leukemia is a relatively uncommon cancer with an incidence of approximately 4/100 000 in Canada [1]. The incidence of AML appears to be declining slightly over the past three decades. Despite treatment advances in recent years, most patients will die of their leukemia. Acute promyelocytic leukemia has a better prognosis and different therapy and is considered separately.

Diagnosis

The French-American-British (FAB) classification system is used to diagnose and classify AML [2]. According to this system the criteria for diagnosis is $\geq 30\%$ blasts. The World Health Organization (WHO) proposed a new classification, which lowers the requirements to 20% blasts [3]. This effectively eliminates the FAB diagnosis of refractory anemia with excess blasts in transformation (RAEB-T). The FAB classification divided AML into 8 subtypes based predominantly on morphology:

Subtype	Name	Description
M0	Myeloblastic, minimally differentiated	
M1	Myeloblastic, without maturation	
M2	Myeloblastic, with differentiation	Typically with t(8;21) – good risk
M3	Promyelocytic	See APL policy
M4	Myelomonocytic	Hepatosplenomegaly, hypokalemia, CNS involvement
M5	Monocytic	Hepatosplenomegaly, hypokalemia, CNS involvement
M6	Erythroleukemia	
M7	Megakaryoblastic	Lower response to induction

- ❖ AML with recurrent genetic abnormalities
 - AML with t(8;21)-AML/ETO
 - AML with abnormal bone marrow eosinophils-inv(16) or t(16;16)
 - APL-t(15;17) and variants
 - AML with 11q23 abnormalities
- ❖ AML with multilineage dysplasia
- ❖ AML and MDS-therapy related
- ❖ AML not otherwise categorized

Baseline Investigations

The following investigations are indicated for most patients with AML:

- ❖ Bone marrow aspiration with cytogenetic analysis
- ❖ CBC, differential, blood film
- ❖ Serum electrolyte and creatinine
- ❖ INR, PTT
- ❖ Serum uric acid
- ❖ Liver function tests
- ❖ Group & Screen



Cardiac Assessment

A clinical cardiac assessment should be performed in all patients potentially eligible for aggressive induction therapy. A MUGA scan or 2D-echocardiogram should be performed in all patients with a history of:

- ❖ Age > 60
- ❖ Hypertension
- ❖ Congestive heart failure
- ❖ Peripheral vascular disease
- ❖ Cerebrovascular disease
- ❖ Angina
- ❖ Cardiac arrhythmia
- ❖ Myocardial infraction

Anthracyclines should be **used with caution** in patients with an EF < 45%, recent MI (< 3 months) or severe arrhythmia.

Prognosis & Staging

The following factors are strongly predictive of poor outcome in AML:

- ❖ Age > 60
- ❖ Karyotype
- ❖ Prior chemotherapy, myelodysplasia, or myeloproliferative disorder (secondary)

Karyotype

The MRC divided patients with AML into 3 risk categories based on karyotype [4].

Risk Group	Karyotype	CR (%)	5 yr OS (%)
Good	t(8; 21), t(15; 17), inv (16)	91	65
Intermediate	Normal, +8, +21, +22, del (7q), del (9q) t(11; q23) other structural/numerical abnormalities	81	41
Adverse	-5, -7, del (5q), abnormal 3q	63	14

Treatment

Most patients with AML should be offered aggressive induction chemotherapy. Palliative supportive treatment may be appropriate for selected patients with co-morbid medical problems, secondary AML or with poor performance status (**see AML in the elderly and palliative treatment**).

Induction Chemotherapy

Induction is the chemotherapy administered in an effort to produce a remission.

Age < = 60 years

Patients are given the 7+3 regimen consisting of daunorubicin 60 mg/m² IV push for 3 days and cytarabine (Ara-C) 200 mg/m²/day by continuous infusion over 7 days (**Appendix B**) [5]. Patients will remain hospitalized until completion of chemotherapy, but may be considered for early discharge (**see below**) [6].



Age 60-80 years

The published evidence on management of AML in the elderly is summarized in **CCO-PEBC EBS 6-14** at www.cancercare.on.ca. Patients over age 60 years derive less benefit from therapy than younger patients and are at higher risk of toxicity. Aggressive antileukemic therapy will be offered to patients with low-risk or intermediate-risk cytogenetics, good performance status and no significant co-morbidities. Patients should be informed of the risks and the relatively limited expectations of treatment.

For patients treated with aggressive intent, daunorubicin 60 mg/m² IV push daily for 3 days and Cytarabine 100 mg/m² by continuous infusion daily for 7 days will be used. Patients who are not eligible for aggressive antileukemic chemotherapy should still be offered active supportive treatment. This should include transfusion, antibiotics and cytoreductive treatment if WBC > 10 or patients have symptomatic organomegaly or organ infiltration. First-line cytoreductive treatment consists of hydroxyurea 1-4 g PO OD. If hydroxyurea is insufficient or if toxicity occurs (mucositis, skin ulcers) add or substitute ARA-C 15-30 mg SC daily or VP-16 100 mg PO OD. If this is insufficient, ARA-C 30-100 mg IV daily by continuous infusion can be administered.

LP Criteria

Patients with initial WBC > 40 x 10⁹/L (or leukemic blasts expressing CD56) should have a diagnostic LP performed on Day 7-8 of induction, after blasts have cleared from the blood, with cytarabine 70 mg given intrathecally (IT). If CNS is positive, LP + IT chemotherapy should be given twice weekly until clear.

Documentation of Remission

A bone marrow aspirate will be performed at day 28-35 after beginning chemotherapy or upon engraftment (ANC > 0.5; Platelet count > 100), which ever comes first. Patients who obtain a complete remission (< 5% blasts) will proceed onto consolidation. Patients who achieve a PR (5-10% blasts) may receive a second course of 7+3. Those who fail to achieve a PR may elect palliative treatment or may be treated with NOVE (**Appendix B**) [7].

HLA Typing

Patients under age 70 should undergo HLA testing for consideration of allogeneic transplantation. Testing should include the patient, siblings, parents and children. Patients up to age 55 may be eligible for allogeneic BMT. Patients between 55-70 may be eligible for non-myeloablative BMT.

Consolidation

Age < 60

A. Intermediate- and Adverse-Risk Cytogenetic

Consolidation consists of 2 cycles of HIDAC (Daunorubicin 45 mg/m²/day x 2 days, cytarabine (Ara-C) 3000 mg/m² IV over 3 hours, q12h on days 1, 3 & 5) for patients ≤ age 60 (**Appendix B**) [8]. Since HIDAC can initiate an inflammatory response, supportive care during HIDAC consolidation should include celecoxib 100 mg po BID x 5 days and Predforte eyedrops QID x 7 days. Each cycle is given 2 weeks after count recovery from the last cycle of therapy. Consolidation is given either on an inpatient or outpatient basis. Criteria for considering outpatient consolidation include:

- ❖ Appropriate IV access
- ❖ Distance ≤ 1 hr from hospital
- ❖ Afebrile with no documented infection
- ❖ Caregiver readily available
- ❖ Available to attend outpatient transfusion 2-3 x/week



B. Good-Risk Cytogenetics

Patients with good risk cytogenetic changes and their associated molecular abnormalities (t(8;21)/AML1-Eto and inv(16)/CBFB-MYH11; known collectively as 'CBF AML') enjoy superior long-term disease-free survival following treatment with chemotherapy. However, realization of this improved prognosis appears to be contingent upon delivery of repeated cycles of high-dose AraC consolidation chemotherapy [9]. Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered. While the optimal number of such cycles remains to be defined, at least three are probably required [9]. For such patients under age 60 y we use three cycles of HiDAC + daunorubicin as outlined above. For patients > 60 y the dose of AraC is reduced to 1.5 g/m² x 6 doses (Q12h days 1, 3, 5).

Age > 60

Patients over the age of 60 with standard or poor-risk cytogenetics do not benefit from high-dose cytarabine consolidation [7]. Patients who enter remission and continue to have a good performance status should receive 2 cycles of consolidation:

❖ Cycle 1 (7+3)

- Daunorubicin 60 mg/m² IV push daily x 3 days
- Cytarabine 100 mg/m² by continuous infusion x 7 days (by ambulatory infusion pump)

❖ Cycle 2 (NOVE)

- Mitoxantrone 10 mg/m²/day x 5 days
- Etoposide 100 mg/m²/day x 5 days

Consolidation for older patients may be given either as an inpatient or outpatient (criteria same as younger patients).

Patients with Left Ventricular Dysfunction

If left ventricular function is impaired amsacrine 100 mg/m² IV x 5 days or etoposide 100 mg/m² daily x 5 days may be substituted instead of daunorubicin. In patients > 60 y MUGA scans should be done prior to each consolidation cycle. If LVEF 40-49% or if LVEF has declined > 10% from baseline, amsacrine 100 mg/m² IV x 5 days should be substituted instead of daunorubicin. If LVEF < 40%, the patient should receive AraC 1.5 g/m² IV x 6 doses (Q12h days 1, 3, 5) with no anthracycline or amsacrine.

Supportive Care

Central Line Care: Patients treated as outpatients should have a dressing change once weekly and should have both lumens flushed at least once/week.

Growth Factors: G-CSF support does not reduce mortality, but can reduce the number of febrile days and days in hospital [10]. G-CSF support will not be used routinely if early discharge during the cytopenic phase is not planned. For patients who will be discharged early after either induction or consolidation, G-CSF 300 µg s/c daily should be given beginning day 7 and continuing until ANC > 1.0.

Transfusion Support: Patients will be transfused to keep hemoglobin > 80 and platelet count > 10. Patients considered for allogeneic transplantation should receive CMV negative products.

Hospitalization: Induction chemotherapy should be initiated in hospital in all patients. Patients may be considered for early discharge at day 8 if they meet the criteria on page 5. Consolidation may be administered as an outpatient in patients who meet the same criteria. Indications for readmission include volume depletion, excessive transfusion requirements, patient's wishes and febrile neutropenia. Patients with AML **are not** candidates for oral outpatient antibiotic therapy for febrile neutropenia.



Post Remission Therapy

The role of high dose therapy for AML in first complete remission remains unclear [11]. Neither autologous nor allogeneic transplantation have been proven to improve survival in all patients, but subgroups may benefit. Patients with good risk karyotypes [t(8:21) inv(16)] will undergo molecular monitoring every 3 months and will be referred for transplant opinion only for molecular or clinical evidence of progression. Patients \leq age 65 with intermediate or high-risk karyotype should be referred for a stem cell transplant opinion.

Stem cell transplantation

The roles of autologous and allogeneic stem cell transplantation in the treatment of AML remain controversial. There have been no trials in the field of allogeneic BMT in which patients with a matched sibling donor have been randomized between allogeneic BMT vs chemotherapy. In the absence of a true randomization, genetic randomization is an established way of comparing allogeneic BMT with chemotherapy or ABMT. In this approach, the outcomes of patients for whom an HLA matched sibling donor is available are compared with outcomes of patients lacking a sibling donor, on an intent-to-treat basis. Five trials of AML post-remission therapy analyzed in this way have been published. These data lead to several generalizations:

1. No advantage in overall survival is shown for the 'donor' over the 'no donor' group in any trial.
2. Subgroup analysis suggests that neither allogeneic nor autologous transplantation is indicated in first CR in patients with a good risk karyotype.
3. For the poor risk cytogenetic group, results with chemotherapy alone are uniformly poor and allogeneic BMT may offer the best chance for long-term survival.
4. Evidence for patients with intermediate risk karyotype remains equivocal.

In the absence of exhaustive evidence-based rules, it is incumbent upon the treating physician to weigh risks for each individual patient, including disease factors, patient factors (especially chronological and biological age), and patient preference in judging if that patient should be referred for consideration of allogeneic BMT.

Although autologous stem cell transplantation is routinely practiced in the UK as postremission therapy for AML, experience in Toronto has not been favourable, and ASCT is currently used only in the context of relapsed acute promyelocytic leukemia.

Special Circumstances

(a) Secondary AML

Patients who develop AML after a history of myelodysplasia, myeloproliferative syndrome or who have previously received chemotherapy have a very poor prognosis often with complex or poor risk cytogenetic abnormalities. Such patients should be considered for allogeneic transplantation and should have HLA typing performed. If transplantation is a possibility, induction therapy should be offered. If transplantation is not an option, palliative chemotherapy should be considered, particularly in patients with high-risk karyotype.

(b) Palliative Therapy

Patients who are not eligible for aggressive antileukemic chemotherapy should still be offered active supportive treatment. This should include transfusion, antibiotics and cyto-reductive treatment if WBC $>$ 10 or patients have symptomatic organomegaly or organ infiltration. First-line cyto-reductive treatment consists of hydroxyurea 1-4 g PO OD. If hydroxyurea is insufficient or if toxicity occurs (mucositis, skin ulcers) add or substitute ARA-C 15-30 mg SC daily or VP-16 100 mg PO OD. If this is insufficient ARA-C 30-100 mg IV daily by continuous infusion can be administered.



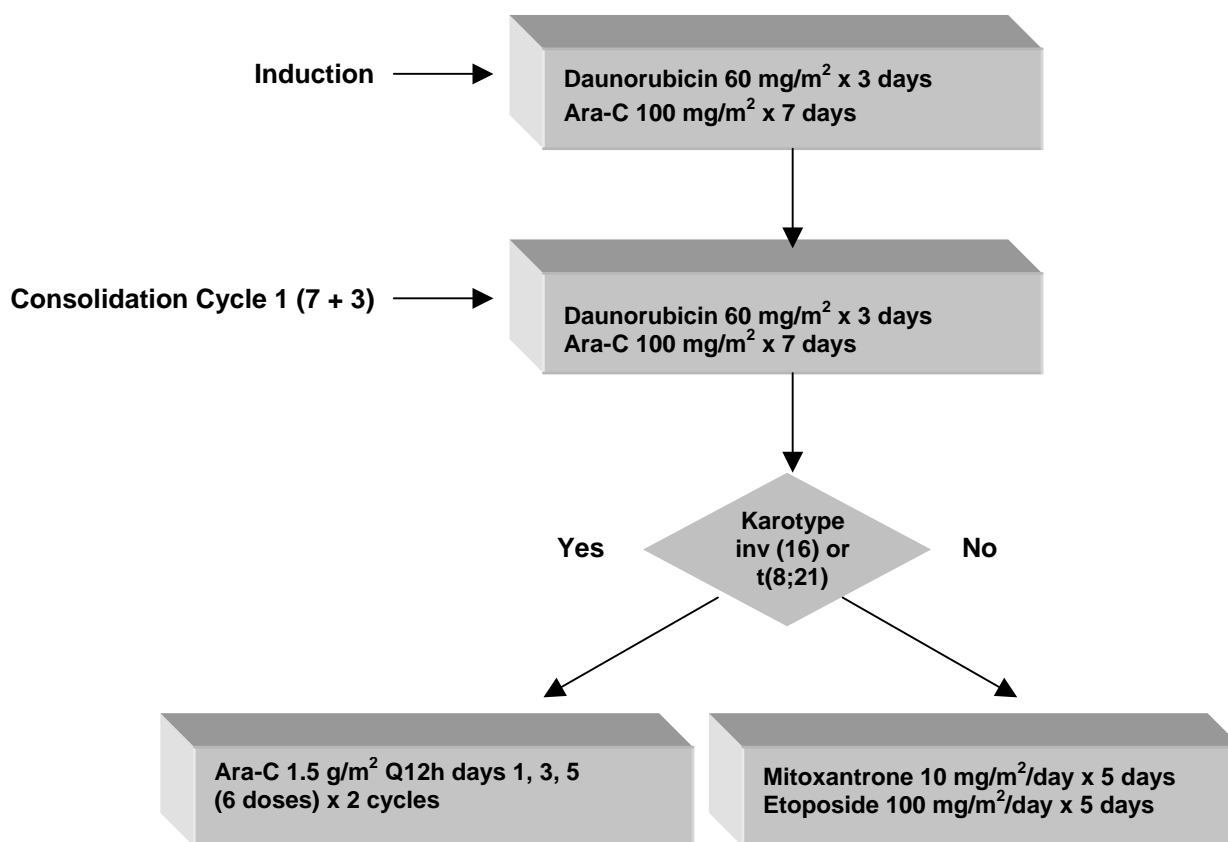
Follow-Up

The frequency of follow-up should be dictated by the risk of relapse and the potential for curative second-line therapy. A follow-up protocol appropriate for most patients would be a history and physical examination, complete blood count and differential (CBC & Diff) every four months for the first two years following documentation of remission, every six months from years two to five and yearly after five years. All or some of this follow-up can take place with the family physician as appropriate. Bone marrow aspirates or biopsies will not be performed routinely unless there is evidence of potential relapse.

Management of Relapse

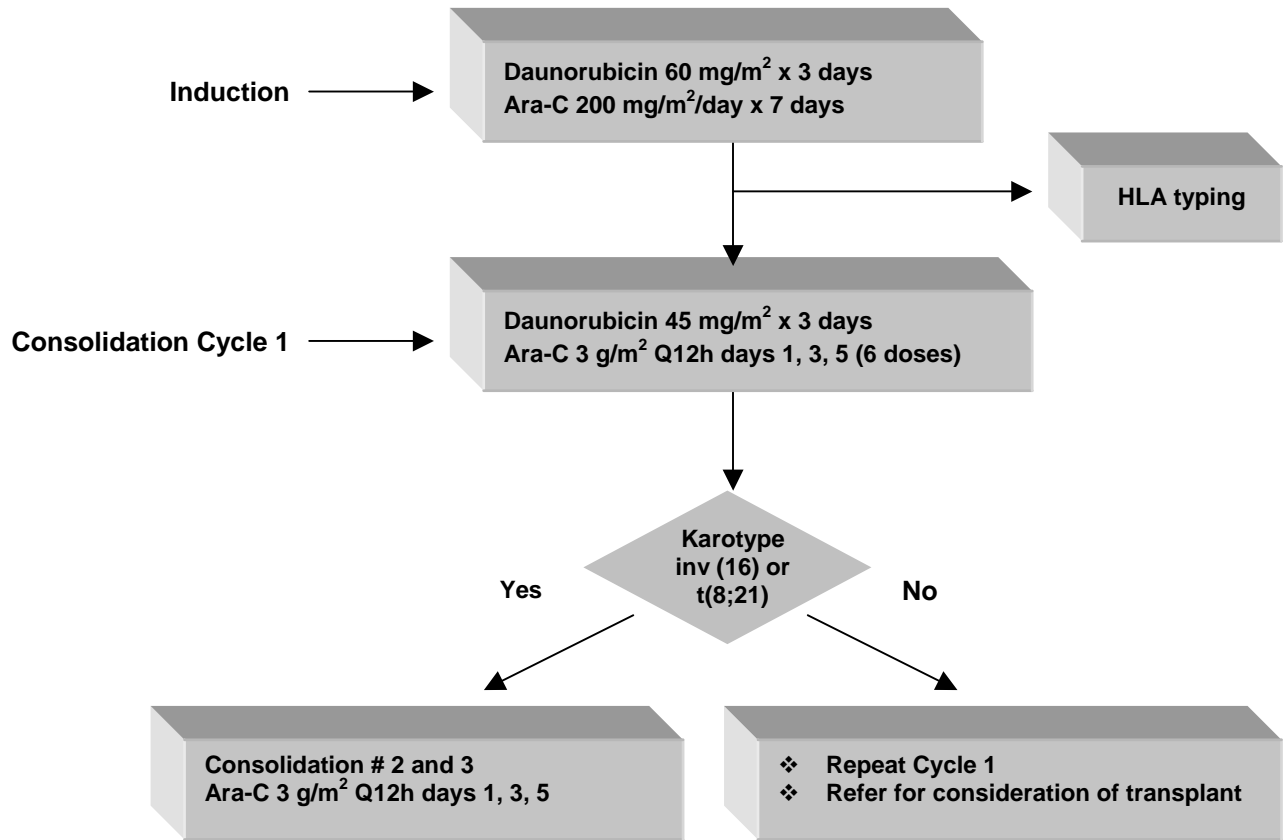
Patients who relapse ≥ 12 months after initial diagnosis can be retreated with 7+3 induction and should be considered for allogeneic or autologous transplantation soon after obtaining second remission. Patients who relapse within one year have a poor prognosis and should be considered for clinical trials or palliative supportive care. If aggressive antileukemic therapy is to be offered, our regimen consists of mitoxantrone 10 mg/m² x 5 days, VP-16 100 mg/m² x 5 days, ara-C 1.5 g q 12H days 6 & 7.

AML Algorithm (Age 60-80 years)





AML Algorithm (Age ≤ 60 years)



References

1. *Canadian Cancer Statistics*. 1999.
2. Bennett, J.M., et al., *Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group*. *Ann Intern Med*, 1985. **103**(4): p. 620-5.
3. Harris, N.L., et al., *World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997*. *J Clin Oncol*, 1999. **17**(12): p. 3835-49.
4. Grimwade, D., et al., *The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties*. *Blood*, 1998. **92**(7): p. 2322-33.
5. Yates, J., et al., *Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study*. *Blood*, 1982. **60**(2): p. 454-62.
6. Allan, D.S., et al., *Outpatient supportive care following chemotherapy for acute myeloblastic leukemia*. *Leuk Lymphoma*, 2001. **42**(3): p. 339-46.
7. Bishop, J.F., et al., *A randomized study of high-dose cytarabine in induction in acute myeloid leukemia*. *Blood*, 1996. **87**(5): p. 1710-7.
8. Mayer, R.J., et al., *Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B*. *N Engl J Med*, 1994. **331**(14): p. 896-903.
9. Byrd, J.C., et al., *Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered*. *J Clin Oncol*, 1999. **17**(12): p. 3767-75.



10. Heil, G., et al., *A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group.* Blood, 1997. **90**(12): p. 4710-8.
11. Imrie, K., et al., *Autologous bone marrow transplantation for acute myeloid leukemia.* Stem Cells, 1996. **14**(1): p. 69-78.