



Guidelines for the Management of
**Acute Myelogenous
Leukemia in Adults**



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Objective:

This guideline reviews the overall management (from initial presentation and diagnosis through referral, treatment and follow up) of adult acute myelogenous leukemia in Nova Scotia. This guideline was written for an audience of *general practitioners and medical students*, not necessarily hematologist specialists. As such, it is a synthesis of knowledge and evidence, and reflects the practice policies of the Hematology/Leukemia Cancer Site Team in Nova Scotia (see Appendix III).

Patients, family members and other non-health professionals are encouraged to review materials written specifically for them. The Canadian Cancer Society Information Service (1-888-939-3333 or www.cancer.ca) is one source for this type of information.

Preamble Note:

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. However, guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision. This guideline will be revised, from time to time, as new evidence becomes available. The current version of this guideline is available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca) The development of this guideline is described in Appendix III.

Comment on Clinical Research:

An important component of treatment decision-making for any patient is the potential for enrollment in relevant clinical research. The Hematology Cancer Site Team is committed to advancing patient care, through participation in clinical trials and other clinical research projects. At any point in time, there may be a clinical trial or other clinical research opportunity related to any component of this guideline. As specific trials or clinical research projects become available, eligible patients may be offered the opportunity to enroll in the relevant trial or research project. Every effort will be made to accommodate patients for clinical research participation, but there will be eligibility restrictions for each trial. Patients are encouraged to discuss clinical trials opportunities with their cancer specialist. Other researchers may also contact patients to offer participation in relevant trials. Current clinical trials are listed on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

Acknowledgements:

This guideline was written by a collaborative effort of the Hematology Cancer Site Team, and was sponsored by *Cancer Care Nova Scotia*. The guidelines incorporate knowledge of current evidence by the cancer experts in Nova Scotia.

For further information on this, or any other Practice Guideline, please contact the CST Co-Chairs, or members of the Guidelines Resource Team, *Cancer Care Nova Scotia* (contact person Michele Moore, Tel. 902-473-3152 or by email michele.moore@ccns.nshealth.ca).

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Guideline Approvals:

- Hematology Cancer Site Team-
 - Initial date approved- 7 Sept 2004
 - Revision with Community Reviewer Input- 4 Jan 2005
- *Cancer Care Nova Scotia*, Commissioner- 16 Feb 2005

Recommended citation:

Robinson SK, Broadfield L. Guidelines for the Management of Acute Myelogenous Leukemia. Hematology Cancer Site Team, *Cancer Care Nova Scotia*, 2005

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Part 1. Introduction

1.1 Risk Factors

The incidence of all acute leukemias in Canada is 2.9 males and 2.3 females per 100,000 persons. In adults, acute myelogenous leukemia (AML) represents about 90% of all acute leukemias.

The incidence rises with age, occurring rarely before age 40 (<1 in 100,000), and increasing to an incidence of 16 cases per 100,000 by age 75. The median age at diagnosis is 65 years.

The etiology of AML is still largely unknown. Genetic, drug, environmental, and occupational factors have been identified as potentially leukemogenic, but most patients present with *de novo* AML. Risk factors associated with the development of AML include benzene exposure, ionizing radiation, and prior exposure to cytotoxic chemotherapy (particularly alkylating agents used for treatment of cancer, connective tissue disease, or immune disorders).

Individuals with constitutional genetic defects, such as Down's syndrome and Klinefelter's syndrome, have an increased incidence of AML. Other genetic disorders associated with chromosomal instability and increased chromosome breakage, such as Fanconi's anemia, Bloom's syndrome, ataxia telangiectasia, and germline *TP53* mutations, are also associated with increased incidence of AML.

AML may result from transformed preleukemic cells, such as those found in myelodysplastic syndromes (MDS). The MDS are a group of clonal, stem cell disorders characterized by refractory cytopenias, dysplastic changes in the bone marrow, and a likelihood of transformation to acute leukemia. The

prevalence in persons >65 years is estimated to be 0.1%. The median age at diagnosis is 70. Risk factors associated with the development of MDS are the same as for AML, however the majority of patients present with *de novo* disease.

Other clonal disorders of the hematopoietic stem cell may develop into AML. These clonal disorders include the following:

- myeloproliferative disorders
 - chronic myelogenous leukemia
 - polycythemia vera
 - essential thrombocythemia
 - agnogenic myeloid metaplasia
 - paroxysmal nocturnal hemoglobinuria
- aplastic anemia

1.2 Pathogenesis

AML is believed to be caused by the malignant transformation of a single hematopoietic stem cell. Leukemic cells are characterized by clonal proliferation and/or a block in normal differentiation and maturation. Clonal hematopoiesis persists in about 30% of patients who achieve clinical remission following treatment. The pathogenesis of AML is a multi-step process, with an initial transformation event in a hematopoietic stem cell followed in clonal descendant cells by additional genetic abnormalities.

Leukemic transformation may occur at an early stage of hematopoiesis with the pluripotent stem cell, or, less often, with a committed stem cell. Differentiation commitment and the degree of maturation are seen in the leukemic phenotype. Phenotypic variants have distinctive clinical and cytogenetic associations.

The pathogenesis of acute leukemia also includes a critical role for oncogenes and anti-oncogenes. About 20% to 30% of leukemia cases are associated with mutations of the *RAS* oncogene, the most commonly detected molecular abnormalities in AML. Control of the proliferation and differentiation of many types of cells involves *RAS* gene products.

In summary, leukemogenesis appears to be a multistep process involving a susceptible hematopoietic cell, a genetic event (oncogenes, chromosomal translocations), and possibly environmental influences (chemical, radiation).

1.3 Clinical Presentation

A decrease in production of normal hematopoietic cells and the proliferation and accumulation of leukemic cells in the bone marrow, blood, and in extramedullary sites are largely responsible for the clinical symptoms.

Common presenting symptoms are:

- weakness, dyspnea on exertion, and fatigue reflecting anemia
- easy bruising, gum or nose bleeding, excessive bleeding following minor injuries or dental/surgical procedures, secondary to thrombocytopenia or coagulopathy. There may also be hypertrophy of the gums (rarely)
- fever and infections, particularly skin and pulmonary infections, secondary to neutropenia or leukopenia
- malaise and anorexia, usually without weight loss

Up to 20% of patients present with marked elevation of white blood cell (WBC) counts (usually exceeding $100 \times 10^9/L$). These patients may develop a hyperleukocytosis syndrome requiring

prompt treatment. Clinical manifestations from leukocyte microthrombi include:

- dizziness
- stupor
- dyspnea
- priapism
- pulmonary insufficiency
- intracerebral and pulmonary hemorrhage

About 5% of all leukemic patients will have asymptomatic central nervous system (CNS) involvement (based on results from cerebrospinal fluid cytology). The risk of CNS involvement in AML is highest in patients with high circulating blast counts, elevated lactate dehydrogenase (LDH) activity, and the monocytic variants of AML.

Part 2. Diagnosis

2.1 Initial Diagnosis

The initial work-up focuses on identifying the type of leukemia and obtaining information from the patient on any co-morbid medical condition, which could affect the patient's ability to tolerate therapy and to assist in treatment decisions.

History and Physical Examination

A thorough history and physical examination are required for diagnosis of acute leukemia. In the history, common presenting symptoms are fatigue, easy bruising and frequent infections.

Examination may reveal pallor and signs of hemorrhage (oral hemorrhagic bullae, petechiae, and ecchymoses). Gingival hyperplasia, lymphadenopathy, hepatosplenomegaly, and skin infiltration (leukemia cutis) may be observed, which are more common in the monocytic subtypes of AML (FAB M4 & M5). Chloromas, which are extramedullary tumors formed by collections of myeloblasts and granulocytes, may present as subcutaneous masses.

Peripheral Blood Findings

A complete blood count (CBC) and differential is essential for diagnosis. Patients may present with a total WBC which is elevated, within the normal range, or below the normal range. Five to twenty percent of patients will present with markedly elevated WBC ($>100 \times 10^9/L$). Blast forms are nearly always present on examination of the peripheral smear. A small percentage of patients may present without circulating leukemic cells. Auer rods, rodlike cytoplasmic inclusions seen in some blasts, are unique to AML. Most patients with AML present

with anemia and/or thrombocytopenia.

Bone Marrow Findings

Aspiration and biopsy of bone marrow, usually from the superior posterior iliac spine, is routinely performed by the hematologist to confirm the diagnosis of acute leukemia. Aspirate samples are sent for morphologic, histochemical, immunophenotypic, cytogenetic, and molecular analysis to enable classification of the leukemia.

Other Work-up Investigations

Hyperuricemia is the most common biochemical abnormality during treatment of acute leukemia. It generally results from the high turnover rate of the proliferating leukemic cells and can lead to urate precipitation, obstructive uropathy, and acute renal failure. Tumour lysis syndrome may occur with initiation of treatment as a complication of intensive cytotoxic chemotherapy or in patients with rapidly rising or very high blast counts. This may result in potentially life-threatening metabolic complications, including hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. All patients should receive vigorous intravenous hydration and therapy with allopurinol prior to chemotherapy.

Disseminated intravascular coagulation (DIC) is common at presentation for leukemic patients, with subtype FAB M3 (acute promyelocytic leukemia). Coagulation screening is performed at initiation of workup. A positive DIC screen would typically have a prolongation of the INR (International Normalized Ratio) and partial thromboplastin times, elevated d-dimer and decreased fibrinogen levels.

This is usually associated with thrombocytopenia and red blood cell fragments in the peripheral blood smear. Multiple blood products and clotting factor replacements are usually needed to manage the DIC, and it usually resolves within a few days.

A thorough cardiac work-up is not usually required, except for patients with cardiac risk factors, based on the patient history, family history, or a previous exposure to anthracycline agents for treatment of any prior malignancy. A baseline scan for cardiac function (i.e. MUGA scan) is generally included in the workup.

Human lymphocyte antigen (HLA) typing should be done in all newly diagnosed AML patients. The typing is usually done at the time of initial diagnostic workup. This information is useful should HLA-matched platelets be needed at some point in patient care, or to assist in pursuing an HLA-matched donor if an allogeneic marrow transplant is considered for subsequent management.

Part 3. Pathology

3.1 Cytochemistry

Histocytochemical staining of bone marrow biopsy samples can distinguish myeloid from lymphoid leukemias, and may help to classify the subtypes of AML:

- Cells of the granulocytic/monocytic lineage stain with myeloperoxidase (MPO). Sudan black B (SBB), and chloroacetate esterase (CAE) may also be used.
- Monocytes alone may be characterized by nonspecific esterase (NSE) staining.
- Lymphoid and erythroid cells are stained with Periodic acid-Schiff reaction (PAS) stains.
- Lymphoblasts, and about 20% of myeloblasts may be tested with terminal deoxynucleotidyltransferase (TdT). TdT is a nuclear enzyme detected by immunofluorescence or immunoperoxidase techniques.

3.2 Immunophenotyping

The immunophenotype of bone marrow cells is determined using monoclonal antibodies that recognize myeloid- and lymphoid-specific glycoprotein antigens (referred to as clusters of differentiation or CD) on the surface of normal and leukemic hematopoietic cells. AMLs usually express the following immunophenotypes:

- All AML cells- CD13, CD15, CD33
- Monocytoid AML cells- CD14
- Lymphoid AML cells- common ALL antigen (CALLA or CD10), CD19, CD20, and the T-cell receptor antigen, CD3
- Blast cells (all lineages, particularly primitive cells)- CD34

3.3 Cytogenetics

Since chromosomal abnormalities are associated with specific leukemia subtypes, response to therapy, and prognosis, cytogenetic analysis of bone marrow is an important component of the evaluation of a leukemic patient. How translocated genes are involved with leukemogenesis is not completely understood. The most common cytogenetic abnormalities are described in Table 3.3.

Cytogenetic information is often unknown at the time of treatment initiation. Induction treatment may begin before cytogenetic results are available (using FAB classification), but decisions regarding consolidation are often based on cytogenetic risk groups.

Table 3.3 Cytogenetic Abnormalities in Acute Myelogenous Leukemia

Abnormality	Description
translocation (8;21) (or t(8;21))	<ul style="list-style-type: none">• occurs in about 15% of AML cases• most commonly subtypes M1 and M2• associated with a more favorable response to chemotherapy
translocation (15;17) (or t(15;17))	<ul style="list-style-type: none">• molecular basis of t(15;17) is the fusion of the retinoic acid receptor alpha gene (<i>RARA</i>) on chromosome 17 with the <i>PML</i> gene on chromosome 15 forming a chimeric <i>PML/RARA</i> gene• this translocation may be detected by cytogenetics and/or molecular biology methods• patients with APL and t(15;17) have a high rate of response to differentiation therapy with ATRA
inversion (16) AND translocation (16;16) (or inv(16) AND t(16;16))	<ul style="list-style-type: none">• inversions and translocations of chromosome 16 have been identified in AML subtype M4, with either eosinophilia or abnormal eosinophils• identify a subgroup of patients with a more favorable prognosis
abnormalities in 11q23	<ul style="list-style-type: none">• usually associated with monocytic AML• two subgroups: i) infants; and ii) therapy-related AML in patients previously treated with topoisomerase II inhibitors (e.g. etoposide, teniposide)
deletions in 5q and/or 7q	<ul style="list-style-type: none">• often associated with other chromosomal abnormalities• therapy-related AML in patients previously treated with alkylating agents (e.g. mechlorethamine, cyclophosphamide) or radiotherapy• commonly seen in patients with pre-existing myelodysplastic syndrome

Part 4. Classification

4.1 FAB Classification

Two classification systems are used to categorize AML. The first is the classic French American British (FAB) typing classification, based on morphology and cytochemical characteristics, and immunophenotype of peripheral blood and bone marrow (Table 4.1). The FAB classification defines AML as $\geq 30\%$ blasts in the marrow. It divides AML into eight subtypes.

4.2 WHO Classification

The new World Health Organization (WHO) classification (Table 4.2) defines AML as $\geq 20\%$ blasts in the marrow or blood. Like the FAB classification, is based on cellular morphology, cytochemistry and immunophenotyping, but adds cytogenetic abnormalities and clinical syndromes for disease categorization. The prognostic importance of cytogenetic information supports its inclusion in this classification system. The WHO classification divides AML into 5 subtypes. It includes leukemias which are secondary to myelodysplastic/myeloproliferative syndromes, or to prior treatment with cytotoxic chemotherapy and/or radiotherapy.

These two classification systems both identify the APL classification, where the promyelocytic morphology (FAB M3) correlates with the presence of a specific translocation, t(15;17). The molecular abnormality defined by this cytogenetic characteristic has led to a treatment specific for APL induction and consolidation (see Section 6.3).

Table 4.1 The FAB Classification System for Acute Myelogenous Leukemia

Subtype	Description
M0	Acute Myeloid Leukemia Without Differentiation or Maturation
M1	Acute Myeloid Leukemia Without Maturation
M2	Acute Myeloid Leukemia With Maturation
M3	Acute Promyelocytic Leukemia (APL)
M4	Acute Myelomonocytic Leukemia
M5	Acute Monocytic Leukemia
M6	Erythroleukemia
M7	Acute Megakaryoblastic Leukemia

Table 4.2 The WHO Classification System for Acute Myelogenous Leukemia

Type	Description
Acute myeloid leukemia with recurrent genetic abnormalities	
	Acute myeloid leukemia with t(8;21)(q22;q22); (<i>AML 1(CBFa)/ETO</i>) Acute myeloid leukemia with abnormal bone marrow eosinophils Inv(16)(p13;q22) or t(16;16)(p13;q22); (<i>CBFb)/MYH11</i>) Acute promyelocytic leukemia (AML with t(15;17)(q22;12) (<i>PML/RARa</i>) and variants Acute myeloid leukemia with 11q23 (<i>MLL</i>) abnormalities
Acute myeloid leukemia with multilineage dysplasia	
	Following a myelodysplastic syndrome or myelodysplastic syndrome/ myeloproliferative disorder Without antecedent myelodysplastic syndrome
Acute myeloid leukemia and myelodysplastic syndromes, therapy related	
	Alkylating agent-related Topoisomerase type II inhibitor-related (may be lymphoid) Other types
Acute myeloid leukemia not otherwise categorized	
	Acute myeloid leukemia minimally differentiated Acute myeloid leukemia without maturation Acute myeloid leukemia with maturation Acute myelomonocytic leukemia Acute monoblastic and monocytic leukemia Acute erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis Myeloid sarcoma
Acute leukemia of ambiguous lineage	
	Undifferentiated acute leukemia Bilineal acute leukemia Biphenotypic acute leukemia

From: Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds.). World Health Organization classification of tumours. Pathology and genetics of tumours of hematopoietic and lymphoid tissues. IARC Press, Lyon, 2001.

Part 5. Referral Information for the New Patient Visit

Referral to the Hematology Cancer Site Team at the QEII Health Sciences Centre

A letter of referral and/or a completed QEII Referral Form for Ambulatory Care, and all relevant laboratory reports which have led to suspicion of a cancer diagnosis are the minimal requirements for a referral to the QEII HSC-Hematology Service. Referral calls may be directed to the hematology referrals/booking office at 902-473-3447 (fax 902-473-3910). A referral need not be delayed due to incomplete results from lab tests. For urgent referrals, or for inpatient admission, please page the hematologist on call through the QEII HSC Locating service (902-473-2220) to discuss the referral.

Referral to the Cape Breton Cancer Centre

Referrals to the Cape Breton Cancer Centre may be directed to the referrals/booking office at 902-567-7774 (fax 902-567-7911). For urgent or emergent referrals, please page the appropriate specialist on call through the Cape Breton Regional Hospital Locating service (902-567-8000) to discuss the referral. Pediatric acute leukemia cases are referred to the IWK Health Sciences Centre.

Referral to the IWK Health Centre

Pediatric cancers are not specifically covered within this guideline. For pediatric patients, referral calls to the IWK Health Centre may be directed to the pediatric oncologist on call at 902-428-8888. For the phone consultation, the following information will be requested: name and age of the patient, parent's phone number, relevant history and physical exam,

presumptive diagnosis, and initial laboratory and diagnostic imaging tests (fax test results and summary of history & physical to 902-428-3216). Further diagnostic work-up will be conducted at the IWK Hospital.

Referral Information

Letter of Referral*

A consultation letter highlighting presenting signs and symptoms is required. If there are any test results or reports pending, these should be noted in the referral letter.

Laboratory or Pathology Reports*

- a. All relevant bloodwork
- b. Any other pathology report from a bone marrow aspiration or biopsy if performed prior to referral

Other Information

- a. Any relevant and/or pending consultation reports or lab/pathology reports (please fax pending information to hematology service as soon as possible)
- b. Detailed information on any previous chemotherapy or radiotherapy of current malignancy
- c. Any information on previous malignancies
- d. Information on co-existing medical conditions and allergies

* Specific information which is necessary for proper triage of referrals

Part 6. Treatment

6.1 Principles of Treatment

The goals of therapy for AML are to eliminate the leukemic clone, and to restore normal hematopoiesis. These goals are usually achieved with myelosuppressive chemotherapy and, if successful, the result is a period of bone marrow aplasia followed by recovery of normal, polyclonal hematopoiesis. A complete remission (CR) is defined as the presence of less than 5% blasts in the bone marrow and restoration of normal blood counts. A successful CR is required to cure AML. The length of patient survival correlates with achieving a CR and the duration of the CR. Patients who have refractory disease or do not achieve CR (often with more than one attempt at induction therapy) usually die within 2 to 4 months of diagnosis, due to complications such as infection or bleeding.

Treatment of AML begins with induction therapy (intended to induce a CR), followed by consolidation therapy (intended to prevent relapse). Although a CR from induction therapy is required, the patient must also retain the ability to tolerate the subsequent treatments during consolidation in order to achieve a cure.

The median survival for untreated or refractory AML is usually a few weeks to 2-3 months. Patients who do not receive consolidation therapy will relapse, usually within 6 to 9 months. Despite the use of current induction and consolidation chemotherapy, most patients will eventually relapse and die of acute leukemia. Median survival is about 2 years (for patients < 60 years) and less for older patients.

Approximately 25% to 40% of patients with AML treated with chemotherapy

are alive and free of disease 5 years after diagnosis.

Decision to Treat

The median age at diagnosis of AML is 65 years. Age alone is not a contraindication to treatment, however, patients older than 60 have lower remission rates. Older patients also may present with concomitant medical problems, which can increase treatment-related morbidity and mortality. Treatment should be initiated **promptly** (i.e. within 48 hours of confirmed diagnosis).

6.2 Acute Myelogenous Leukemia

Acute Promyelocytic Leukemia is discussed in section 6.3.

6.2.1 Induction Treatment

Clinical Trials

Since CR rates from induction therapy are about 70% in younger patients and 50% in older patients, there is room for more improvement. Given the rarity of AML, patients should be offered entry into a clinical trial as the preferred treatment strategy. If there is no clinical trial for which the patient qualifies, or if a trial is refused, conventional induction therapy may be considered.

Conventional Induction Therapy

The standard induction regimen for newly diagnosed AML consists of cytarabine (cytosine arabinoside, ara-C) plus an anthracycline, such as idarubicin (or daunorubicin). Continuous infusion of cytarabine at 200 mg/m²/day for 7 days is used with an intermittent infusion of idarubicin at 12 mg/m²/day for the first 3 days. This regimen of "7 + 3" is used at the QEII HSC, as the standard induction regimen. Patients are usually admitted to hospital for 4-6 weeks for induction, to manage complications and side effects.

Monitoring for Response

A marrow examination is usually performed on day 14 of the induction regimen. If there is persistent leukemia, second-line induction treatment should be considered. If there is no evidence of leukemia, the marrow examination will be repeated after recovery of normal blood counts to confirm that the patient has achieved a CR.

Second-line Induction Therapy for Refractory disease

If a CR is not achieved after the first attempt with Idarubicin-Cytarabine (IDAC) induction therapy, a second round of induction chemotherapy may be offered to the patient. Second-line induction therapy may use high dose cytarabine (HDAC) or Mitoxantrone-Etoposide (NOVE) chemotherapy. If this induction fails, a third line induction is sometimes considered. The likelihood of a successful CR is lower with second and third line attempts.

One approach to deal with refractory disease is to use alternate cytotoxic agents for the second induction attempt. NOVE are generally used for second-line induction therapy. Another approach is based on the observation of a steep dose-response curve for cytarabine. Increasing doses of cytarabine, given in doses of 1 to 3 g/m², have been used in an attempt to overcome cytarabine resistance in leukemic blasts and improve remission rates and survival.

6.2.2 Consolidation Chemotherapy

The goal of consolidation therapy is to eliminate residual leukemic cells, prevent relapse, and improve survival. Patients usually receive 2 cycles of consolidation chemotherapy with either IDAC, NOVE, or less often with HDAC. Choice of consolidation chemotherapy regimen, however, is also based upon which

regimen(s) were used for induction, response to induction chemotherapy, and the patient's performance status or ability to tolerate more toxic chemotherapy.

6.2.3 Stem Cell Transplant (SCT)

Allogeneic Stem Cell Transplantation

Allogeneic bone marrow transplantation (allo-BMT) may improve disease-free survival for patients with AML in remission. Allogeneic bone marrow transplantation may be offered to patients \leq 55 years old with related donors who have a compatible HLA tissue type. If there is no related donor available, and if the patient is \leq 50 years old, stem cells from a matched-unrelated donor (MUD) may be considered (if a suitable donor is available). The patient will need to be admitted to hospital during and following the transplantation procedure, particularly for management of adverse effects from the treatment, and from graft-versus-host disease symptoms (see Section 8).

There are several mechanisms by which allo-BMT may cure AML. Marrow-ablating chemo-radiotherapy with supralethal doses, given as the preparative regimen, could eliminate the leukemic clone. Patients are rescued from the marrow ablation by infusion of normal hematopoietic cells from the allogeneic donor. An immunologic effect could contribute to the cure by utilizing the immune cells of the infused donor marrow, which then add to the leukemic cell kill. This is known as the graft-versus-leukemia (GVL) effect. GVHD (graft-versus-host disease) and GVL appear together, although they may be mediated by different subsets of T-cells in the donor graft. Relapse rates are inversely correlated with the degree of GVHD.

Patients between 55 and 65 years who have a related HLA-identical donor may be considered for a non-myeloablative SCT. In this procedure, immunosuppressive but non-myelobalative doses of chemotherapy are given to eliminate most of the leukemic clone and immune cells prior to transplant. The intent of this procedure is to induce a GVL effect with less risk of transplant-related mortality; however leukemic relapse and GVHD remain as problems.

Use of allo-BMT for patients in first remission remains controversial. Some patients may be cured with chemotherapy alone, and the transplant-related mortality is considerable. Randomized studies of patients undergoing allo-BMT in first remission have demonstrated equivalent rates of overall survival despite a decreased relapse rate and a trend towards improved disease-free survival. This is partly due to the higher rate of transplant-related mortality, primarily from GVHD and interstitial pneumonia. In some studies, however, patients who relapsed following conventional post-

remission chemotherapy were successfully treated with allo-BMT.

Allogeneic stem cell transplantation offers the best chance of survival for relapsed or refractory AML patients.

Autologous Bone Marrow Transplantation

Autologous bone marrow transplant (auto-BMT) is less commonly offered to patients with AML in remission, but may be considered.

Prognostic Factors in AML Consolidation Treatment

The decision regarding the optimal post-remission therapy for an individual patient should take into account patient and disease-related prognostic factors (Table 6.2.2).

6.2.3 Induction Failure

Patients are considered to have primary refractory disease when CR is not obtained after two adequate induction attempts. If IDAC chemotherapy was used for the first induction, the HDAC or NOVE regimen should be considered for the second induction attempt. Patients up to 55 years old who fail to achieve remission after a second induction

TABLE 6.2.2 Prognostic Factors in Acute Myeloid Leukemia

Factor	Favorable	Unfavorable
Age	<40 years	>60 years
Leukemia	<i>De novo</i>	Secondary
WBC count	<10 x 10 ⁹ /L	>100 x 10 ⁹ /L
DIC	Absent	Present
LDH	Normal	High
Serum albumin	Normal	Low
FAB type	M3 [t(15;17)], M4Eo	M0, M5a, M5b, M6, M7
Cytogenetics	inv 16, t(8;21) normal	5q-, 7q-, +8
Auer rods	Present	Absent
Courses to complete remission	Single	Multiple

attempt may be considered for one more induction. If remission is still not achieved, best supportive care is all that remains to offer the patient.

6.2.4 Treatment of Relapsed Leukemia

Once the leukemia relapses, patient outcome is poor. The patient may be offered salvage therapy with one of the 3 regimens described above (i.e. IDAC, HDAC, or NOVE) if they are suitably fit. The probability of a second remission correlates strongly with the duration of first remission. Second remissions are always shorter than first.

After achieving a second remission, eligible patients would be considered for an allogeneic SCT, if they have not been given a transplant previously. If re-induction fails, or if the patient is not a candidate for transplant, outcome is very poor and supportive care is all that remains to be offered.

6.3 Acute Promyelocytic Leukemia

6.3.1 Initial Induction

Acute promyelocytic leukemia (APL) is a distinct subtype of AML, characterized by a bleeding diathesis, younger age at presentation, the presence of a balanced translocation between chromosomes 15 and 17, and a unique response to the retinoid differentiating agent tretinoin (all-*trans*-retinoic acid or ATRA). Patients with the APL sub-type of AML may develop DIC, which has been attributed both to the release of procoagulants from the abnormal promyelocytes during chemotherapy-induced cell lysis and to excessive fibrinolytic activity.

Although initiation of conventional induction chemotherapy (cytarabine-anthracycline 7 + 3) or tretinoin results in similar CR rates (about 70%), chemotherapy exacerbates the coagulopathy associated with APL.

Mortality during induction is higher in APL (12% to 14%) than in other subtypes of AML. The risk of fatal hemorrhage (CNS and pulmonary) is associated with high circulating blast and promyelocyte counts, low platelet count, older age, and anemia. It has not been reduced by the use of heparin or antithrombotic therapy.

Tretinoin causes terminal differentiation and the apoptotic death of leukemic cells. Because CR is achieved through maturation and differentiation of the leukemic cell, the usual period of marrow aplasia and the toxicities seen with conventional chemotherapy do not occur with tretinoin. The coagulopathy associated with APL reverses more quickly following initiation of tretinoin therapy. Remissions following tretinoin therapy usually occur at 5 to 6 weeks.

When tretinoin is combined with chemotherapy, CR rates are very high (about 90%), but relapses are more common when these drugs are given concurrently, instead of chemotherapy following the tretinoin. Although tretinoin is highly successful in achieving a CR, if maintained on tretinoin alone, most patients will relapse within a few months. Current treatment of APL includes the use of tretinoin in conjunction with daunorubicin-cytarabine chemotherapy as the induction regimen, followed by 2 cycles of consolidation chemotherapy with daunorubicin plus tretinoin (no cytarabine). This is followed by tretinoin for one year (or until relapse). There is evidence that maintenance with tretinoin or chemotherapy improves survival.

The choice of anthracycline agent and dose have been debated in clinical research. Idarubicin-cytarabine has been used instead of daunorubicin-

cytarabine in some studies. Other studies have examined the role of cytarabine, and conclude that a higher dose of anthracycline and no cytarabine may improve survival and reduce serious complications. An alternative choice for APL treatment may be induction and consolidation with an anthracycline (e.g. idarubicin) and tretinoin only.

A unique and potentially lethal toxicity associated with tretinoin is the retinoic acid syndrome, which has been reported in about 25% of patients within the first 3 weeks of initiation of tretinoin therapy. The retinoic acid syndrome consists of fever, dyspnea, hypotension, edema, weight gain, pulmonary interstitial infiltrates, and pleural and pericardial effusions. This syndrome is often, but not uniformly, preceded by a leukocytosis. The institution of high-dose corticosteroid therapy early in the course of the retinoic acid syndrome results in symptomatic improvement and recovery for most patients.

6.3.2 Treatment of Relapsed Acute Promyelocytic Leukemia

Patients who have not been exposed to tretinoin for at least 6 to 12 months may retain sensitivity to tretinoin, and this should be considered for treatment of relapsed disease. Patients under 65 years of age may be considered either for allo-BMT or auto-BMT after achieving a second remission. Autologous transplantation using molecularly negative cells may result in long-term disease-free survival.

Although there are regulatory restrictions limiting access in Canada, arsenic trioxide has recently been shown to induce morphologic and molecular CR's in 80% of patients with APL who have relapsed following conventional therapy. This agent appears to induce

cytodifferentiation and apoptosis in leukemic cells. Even the leukemic cells from patients who are resistant to retinoids are sensitive to arsenic trioxide. Arsenic trioxide must be used with caution as cardiac arrhythmias may occur; close monitoring of electrolytes and electrocardiogram (ECG) is mandatory. Arsenic may be given alone or with standard induction/consolidation chemotherapy for patients refractory to tretinoin treatment.

Part 7. Follow-up Practice

7.1 Monitoring During Therapy

The number of daily laboratory tests performed during induction therapy should be kept to a minimum, although patients will have daily bloodwork (CBC, ESR, BUN & Creatinine) during the first several days. The bone marrow evaluation is usually repeated once at 14 days from the start of induction to document response (aplasia versus residual disease) and again at the time of hematologic reconstitution to document complete remission or residual disease. Further evaluation may be necessary.

7.2 Post-remission Surveillance

Recommendations for post-remission surveillance include monitoring CBCs monthly for the first 2 years after patients have completed consolidation, then less frequently for 5 years. Bone marrow evaluation is recommended if the hemogram becomes abnormal.

Part 8. Supportive Care Issues

The diagnosis and treatment of AML can be a very frightening and isolating time for patients and their families. Patients will be cared for on a specialized hematology/oncology unit that welcomes family and friends. It often helps if patients bring some items from home to make their stay as comfortable as possible.

A comprehensive multidisciplinary team is available to assist the patient and family during the diagnosis and treatment of this disease. Some of the common side effects that occur during the period of treatment include:

- Stomatitis
- Diarrhea
- Alopecia (temporary, hair usually regrows once the chemotherapy is completed)
- Pancytopenia & infections
- Fatigue

Other side effects may occur in the weeks or months following the treatment, including:

- Sterility and/or treatment-induced menopause
 - Sperm banking will be discussed with male patients prior to initiation of treatment, but this is not always an option

Cancer patients often have various psychosocial needs during treatment and after treatment completion. Support may be available from many different health care professionals, including the inpatient team, the Psychosocial Team of the Cancer Care Program, and other local resources.

In addition to psychosocial supportive care issues, there are several medical interventions recommended for symptom management during treatment of patients with acute

leukemia. Some of these are as follows:

- Antibiotics, antifungals, and/or antivirals, for active infections.
- Empiric broad-spectrum antibiotics for febrile neutropenic episodes (may include antifungals).
- Thorough hand washing before and after patient contact and precise care of central venous catheters, to reduce exposure to pathogens.
- A central venous catheter is placed to facilitate administration of chemotherapy, antibiotics, blood products, other medications, and fluids as well as to permit easy access for blood sampling.
- Blood products:
 - Use CMV-negative blood products if CMV serology is negative or unknown; unscreened if serology is positive.
 - Transfusion thresholds-RBCs for HGB < 8g/dL or symptoms of anemia; platelets for patients with platelet count < $10 \times 10^9/L$ or with any signs of bleeding. These thresholds may be adjusted for some patients.
- If evidence of DIC, give cryoprecipitate to maintain fibrinogen > 1.0 g/L.
- Tumor lysis prophylaxis: allopurinol, hydration with or without diuresis and/or urine alkalinization. More frequent bloodwork (q6-12h) during the period of greatest risk.
- LP is not routinely done, but may be required if symptomatic for neurologic involvement (may also be considered for FAB M5- monocytic AML).
- Patients receiving high-dose cytarabine therapy (particularly those with impaired renal function or patients > 60 years are at risk for cerebellar toxicity. Neurologic assessments including tests for

nystagmus, slurred speech, and dysmetria should be performed before each dose of cytarabine. In patients exhibiting rapidly rising creatinine due to tumor lysis, high-dose cytarabine should be discontinued.

- Steroid eye drops to both eyes daily for all patients undergoing high-dose cytarabine therapy.

Neither routine gut decontamination nor prophylactic antibiotic treatment during induction or consolidation therapy is recommended any longer. All blood products are leukocyte-depleted. It is recommended that all patients be HLA typed initially.

Management of Coagulopathy

DIC, characterized by thrombocytopenia, prolongation of the prothrombin, activated partial thromboplastin, and thrombin times, increased levels of fibrin degradation products, and hypofibrinogenemia occurs in about 30% of patients with AML, most commonly in patients with the acute promyelocytic subtype (M3). The bleeding diathesis associated with APL is often exacerbated by cytotoxic chemotherapy and is associated with a high rate of early mortality, primarily from intracranial hemorrhage.

The use of heparin in the management of these patients remains controversial. Although a number of small, retrospective studies have suggested that the use of prophylactic heparin decreases fatal hemorrhage, in the largest retrospective study published, no benefit with respect to the incidence of hemorrhagic deaths, complete remission rate, or survival could be attributed to the use of heparin.

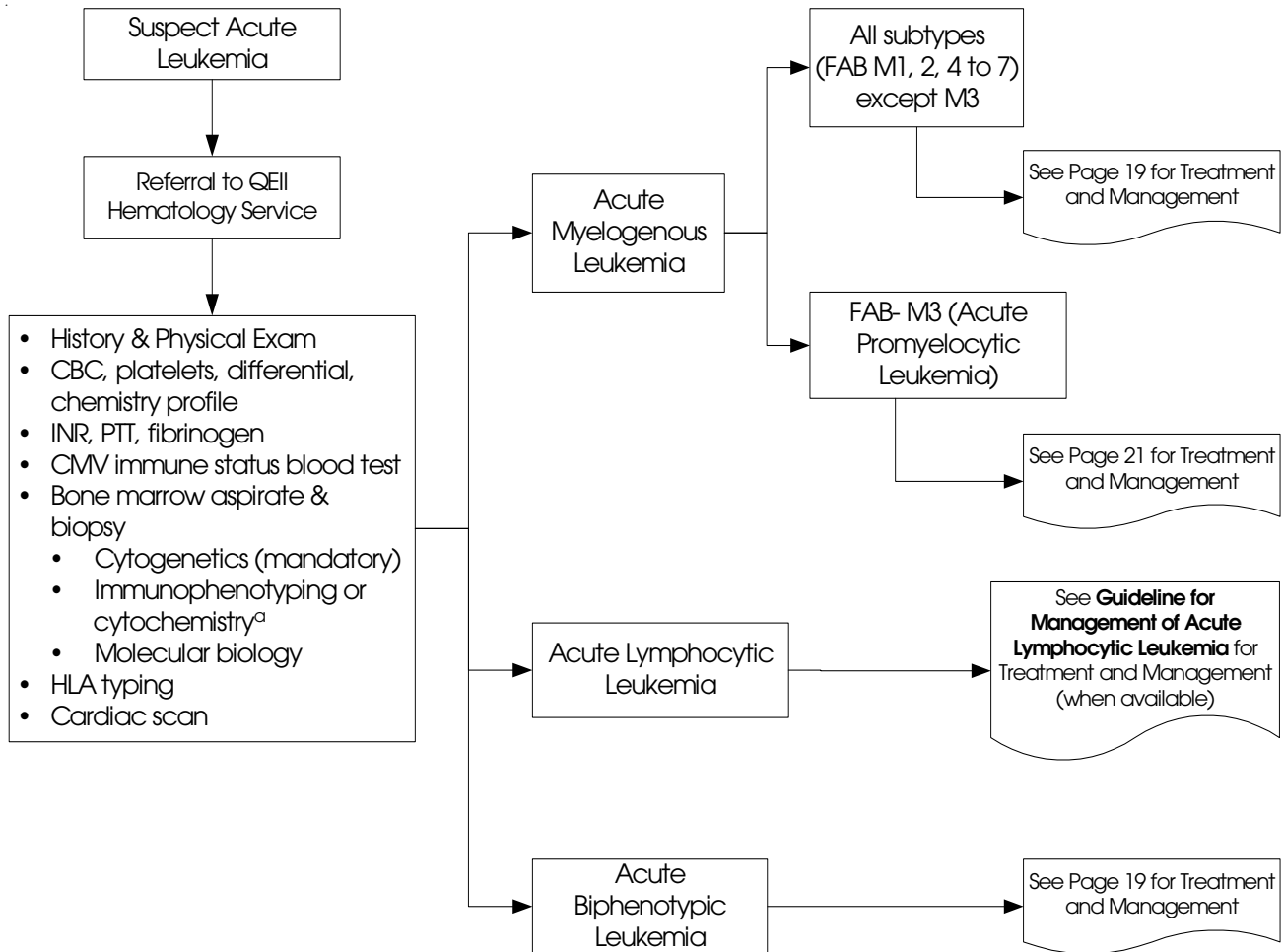
Management strategies include:

- the use of cryoprecipitate to maintain the fibrinogen level above 1 g/dL
- platelet transfusions to maintain the platelet count above $20 \times 10^9/L$ in the absence of active bleeding
- platelet transfusions to maintain the platelet count above $50 \times 10^9/L$ in the presence of active bleeding
- fresh frozen plasma in patients with active bleeding and prolonged prothrombin and partial thromboplastin times

Heparin therapy may be initiated if monitoring of the aforementioned laboratory parameters suggests ongoing consumption despite the earlier listed maneuvers. The use of ATRA does not appear to have altered the risk of hemorrhagic death from APL.

Part 9. Practice Pathways

Work-up and Classification of Acute Leukemia^b

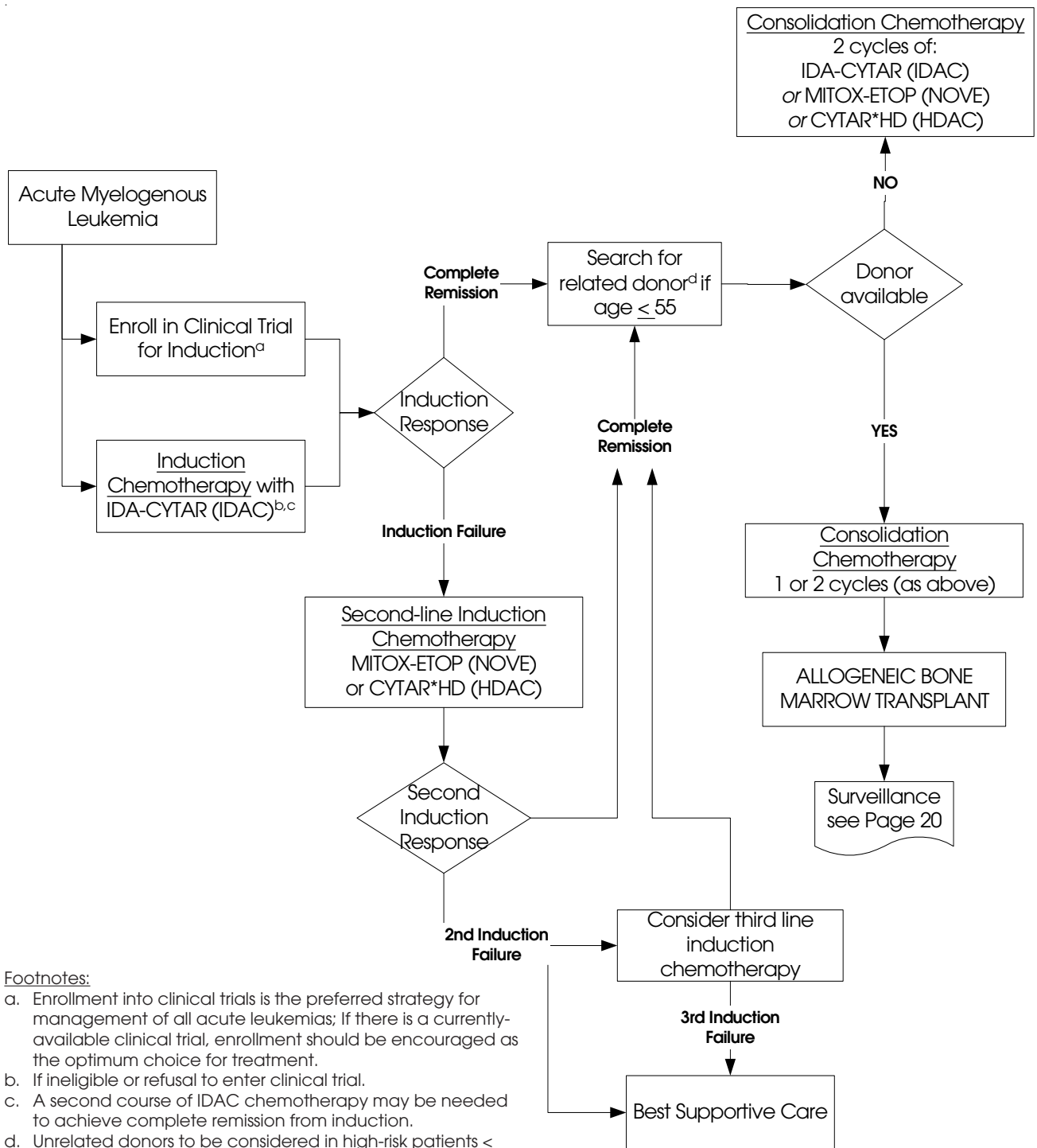


Footnotes:

a Samples for both techniques should be taken at the time of initial sampling. Prioritization of these two complementary diagnostic procedures will be left to the discretion of the pathology department. The role of immunophenotyping in detecting minimal residual disease is as yet untested.

b When presented with rare cases not fitting this algorithm, consultation with an experienced hematopathologist is recommended.

Treatment of Acute Myelogenous Leukemia



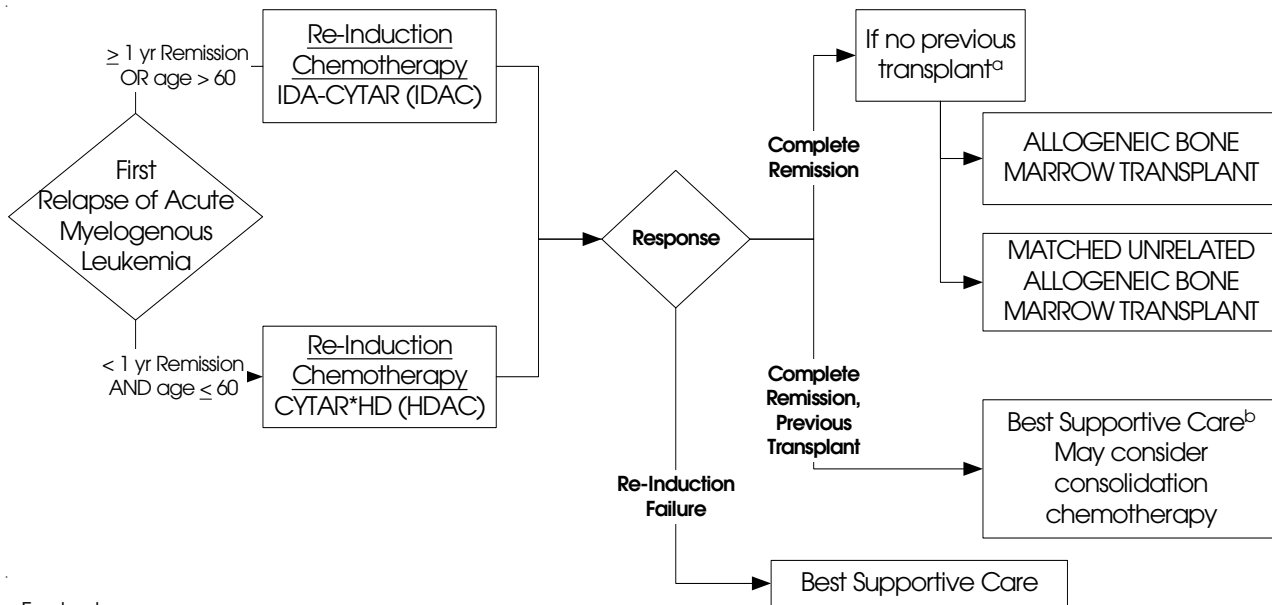
Footnotes:

- Enrollment into clinical trials is the preferred strategy for management of all acute leukemias; If there is a currently-available clinical trial, enrollment should be encouraged as the optimum choice for treatment.
- If ineligible or refusal to enter clinical trial.
- A second course of IDAC chemotherapy may be needed to achieve complete remission from induction.
- Unrelated donors to be considered in high-risk patients < age 50 without family donor.

References:

- Wiernik PH, Banks PL, Case DC Jr, et al.: Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood* 79 (2): 313-9, 1992.
- Bow EJ, Sutherland JA, Kilpatrick MG, et al.: Therapy of untreated acute myeloid leukemia in the elderly: remission-induction using a non-cytarabine-containing regimen of mitoxantrone plus etoposide. *J Clin Oncol* 14 (4): 1345-52, 1996.
- Bishop JF, Matthews JP, Young GA, et al.: A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. *Blood* 87 (5): 1710-7, 1996.
- Anderson JE, Gooley TA, Schoch G, et al.: Stem cell transplantation for secondary acute myeloid leukemia: evaluation of transplantation as initial therapy or following induction chemotherapy. *Blood* 89 (7): 2578-85, 1997.

Treatment of Relapsed Acute Myelogenous Leukemia



Footnotes:

- a. If related donor (e.g. sibling) available and age < 55, consider allogeneic BMT. Unrelated donors may be considered in patients < age 45 without family donor.
- b. All patients who have previously received a transplant or who are not reasonable candidates for transplant, including all patients > 55 years.

Surveillance Post Therapy

Patients who received only chemotherapy

- History, physical examination
- CBC, platelets every month for 2 yr, then less frequently for 5 yr, then every 6 mo up to 10 yr
- Bone marrow aspirate only if peripheral smear abnormal or cytopenias develop

Patients who received a transplant

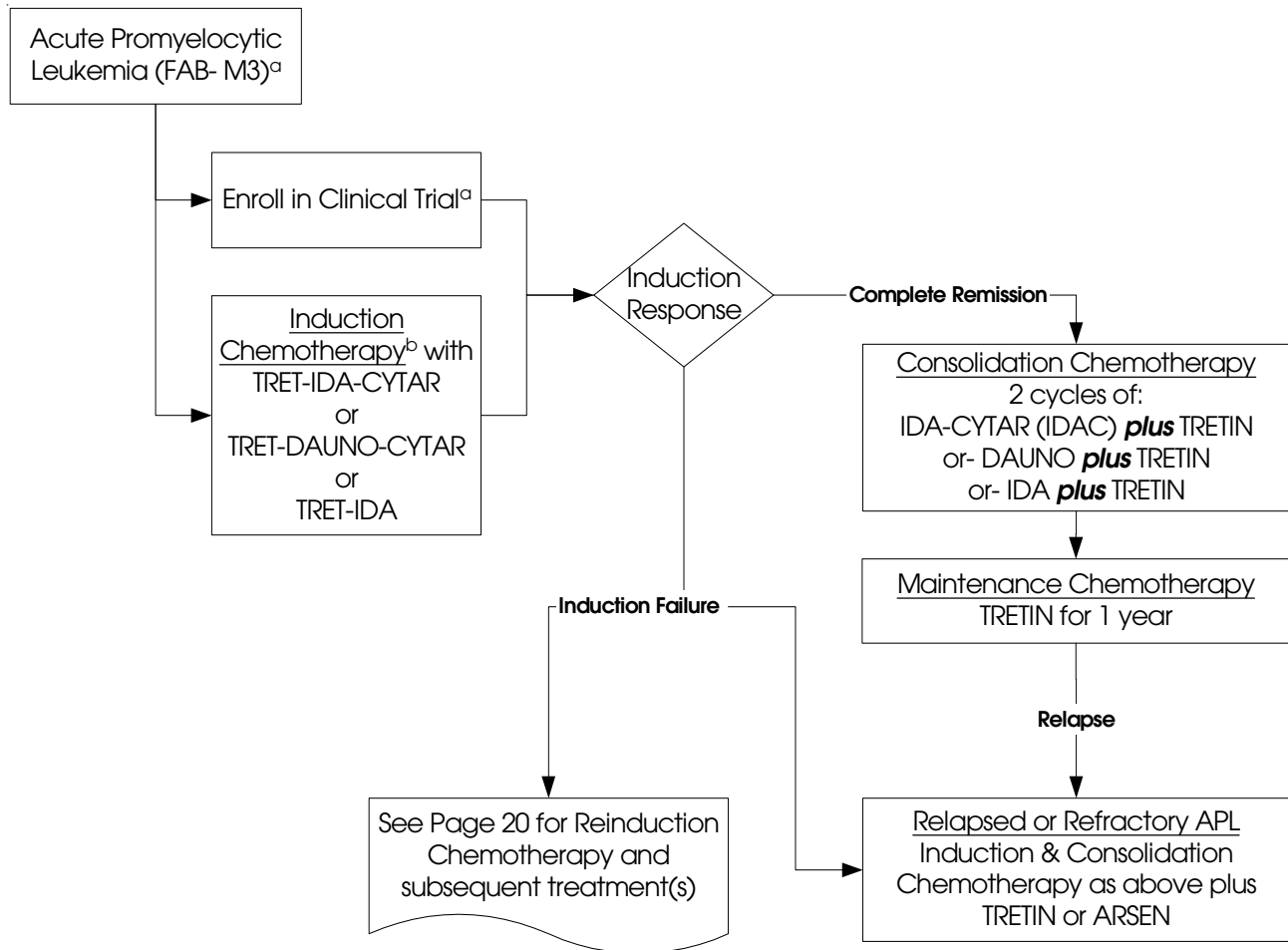
Same as above, plus:

- Screen for symptoms of chronic graft vs. host disease
- Vaccinations as per post-transplant protocol

Supportive Care Measures During Treatment

- Antibiotics, antifungals, and/or antivirals for infections.
- Empiric broad-spectrum antibiotics for febrile neutropenic episodes (may include antifungals).
- Regular use of mouth rinse solution to prevent mucositis.
- Antiemetic agents given with chemotherapy.
- For diarrhea, culture stools and use antidiarrheal agent
- Nutrition maintained with normal diet as tolerated, if possible.
- Blood products:
 - Use CMV-negative blood products if CMV serology is negative; unscreened if serology is positive
 - Transfusion thresholds-RBCs for HGB < 8g/dL or symptoms of anemia; platelets for patients with platelet count < 10 x 10⁹/L or with any signs of bleeding
- If evidence of DIC, give cryoprecipitate to maintain fibrinogen > 1.0 g/L.
- Tumor lysis prophylaxis: allopurinol, hydration with or without diuresis and/or urine alkalinization.
- LP at diagnosis if symptomatic for neurologic involvement (may also be considered for FAB M5- monocytic AML).
- Patients receiving high-dose cytarabine therapy (particularly those with impaired renal function or patients > 60 years), are at risk for cerebellar toxicity. Neurologic assessments including tests for nystagmus, slurred speech, and dysmetria should be performed before each dose of cytarabine. In patients exhibiting rapidly rising creatinine due to tumor lysis, high-dose cytarabine should be discontinued.
- Steroid eye drops to both eyes daily for all patients undergoing high-dose cytarabine (HDAC) therapy.

Treatment of Acute Promyelocytic Leukemia



Footnotes:

- a. Enrollment into clinical trials is the preferred strategy for management of all acute leukemias. If there is a currently-available clinical trial, enrollment should be encouraged as the optimum choice for treatment.
- b. If ineligible or refusal to enter clinical trial.

APPENDIX I

Hematology Cancer Site Team Members

Louis Fernandez, Hematology (Lymphoma/Myeloma Co-Chair)
Sue Robinson, Hematology (Leukemia Co-Chair)
Derek Wilke, Radiation Oncology Lead

David Anderson, Hematology
Deanna Bowley, Pharmacist
Larry Broadfield, CCNS Systemic Therapy Program
Gordon Butler, Psychology
Judith Cleary, Clinical Nurse Educator (on leave)
Colleen Colville, Clinical Nurse Educator (temporary)
Stephen Couban, Hematology
Annette Foyle, Pathology
Jim Godin, Pharmacist
Ormel Hayne, Hematology
Andrea Kew, Hematology Fellow
Ross Langley, Hematology
Heather MacKenzie, Site Team Secretary
Liam Mulroy, Radiation Oncology
Andrew Padmos, Hematology & CCNS Commissioner
Jane Palmer, Manager Medical Day Care
Irene Sadek, Pathology
Cathy Schwindt, Manager Inpatient Hematology (on leave)
Marlene Sellon, Oncology Pharmacy
Chris Skedgel, Health Economist
Cynthia Stockman, Manager Inpatient Hematology (temporary)
Vickie Sullivan, Director Cancer Care Program
Kathleen Walker, Pharmacist
Darrell White, Hematology
Maggie Yuen, Hematology Fellow

There are no known conflicts of interest by this team relevant to this guideline

APPENDIX II

Chemotherapy Regimens

Initial Treatment – AML

IDA-CYTAR*3/7 (IDAC)

Idarubicin 12 mg/m²/day IV x 3 days
Cytarabine 100 mg/m²/day continuous IV x 7 days

CYTAR*HD (HDAC)

Cytarabine 3000 mg/m² IV q12h x 6 days
Inpatient monitoring & supportive care

MITOX-ETOP (NOVE)

Mitoxantrone 10 mg/m² IV daily X 5 days
Etoposide 100 mg/m² IV daily X 5 days

Consolidation Treatment – AML

MITOX-ETOP (NOVE)

IDA-CYTAR*3/7 (IDAC)

CYTAR*HD (HDAC)

Initial Treatment – APL

TRET-IDA-CYTAR

Tretinoin 45 mg/m² PO daily – Until remission or for 90 days
Idarubicin 12 mg/m²/day IV x 3 days
Cytarabine 100 mg/m²/day continuous IV x 7 days

TRET-DAUNO-CYTAR

Tretinoin 45 mg/m² PO daily – Until remission or for 90 days
Daunorubicin 45 mg/m²/day IV x 3 days
Cytarabine 100 mg/m²/day continuous IV x 7 days

TRET-IDA

Tretinoin 45 mg/m² PO daily – Until remission or for 90 days
Idarubicin 12-15 mg/m²/day IV x 4 days

Consolidation Treatment – APL

TRETIN (ATRA)

Tretinoin 45 mg/m² PO daily – For up to 1 year

Note: Tretinoin is not approved in the QEII HSC Formulary for maintenance treatment of APL

Relapse Treatment – APL

TRETIN OR

ARSEN

Arsenic Trioxide 0.15 mg/Kg IV daily –
For up to 60 doses during re-induction or up to 25 doses during re-consolidation

Note: Arsenic Trioxide is not approved as a drug for use by Health Canada; special authorization may be obtained through the Special Access Program to acquire and use this agent. Otherwise, this treatment option is not available.

APPENDIX III **Guideline Development Process**

This guideline was written by a writing team, comprised of Dr. K.S. Robinson and L. Broadfield. Upon completion of an initial draft, the guideline was reviewed by the Hematology/Leukemia Cancer Site Team (CST) members for critical appraisal. Format issues were resolved in collaboration with the Guidelines Resource Team of *Cancer Care Nova Scotia*.

This guideline was written for an audience of *general practitioners and medical students*, not necessarily hematologist specialists. As such, it is a synthesis of knowledge and evidence, and reflects the practice policies of the Hematology/Leukemia Cancer Site Team in Nova Scotia. The written text on management is supported by the graphic flowcharts in the 'Practice Pathways' section.

Once the draft document was approved by the CST, it was distributed to a small group of community reviewers. The draft guidelines were also presented to a meeting of oncology pharmacists from Atlantic Canada. Community reviewers included identified hematologists, internists, pathologists, selected oncology nurses and oncology pharmacists from health care districts in Nova Scotia, New Brunswick, Newfoundland, and Prince Edward Island. 114 copies of the guideline were distributed for review, of which 49 were sent to pharmacists who had attended the earlier presentation of this topic. All responses were anonymous.

Responses to the draft review were collected on a standard guideline review questionnaire. Results are presented on the opposite page. The low response rate from pharmacists is attributed to the fact that this group had previously reviewed the guideline and had provided feedback at that time. The adjusted response rate was 25%, when the pharmacists were removed from analysis.

Upon review of the feedback from the community reviewers, and incorporation of appropriate comments, the guidelines were

returned to the Hematology Cancer Site Team (CST) for final review and approval. The CST-approved document was reviewed by the Guidelines Resource Team against the AGREE tool for guideline evaluation. A number of changes were incorporated into the final guideline document, in better compliance with the AGREE tool domains.

The approved guideline will be circulated in hard copy to all hematology specialists (from multiple disciplines) as well as to the cancer chemotherapy clinics and regional hospital pharmacies in Nova Scotia. It is also planned to distribute this guideline to primary health care professionals (particularly family physicians) as new referrals are made to the hematologists, as a form of just-in-time education. This is based on the principle that adults learn better when knowledge is associated with a current case (problem-based learning). This tactic will be evaluated as it goes along, to test for effectiveness and usefulness. Copies will also be made available to healthcare professionals in Prince Edward Island, Newfoundland, and New Brunswick. Others who are interested may request hard copies by contacting *Cancer Care Nova Scotia (CCNS)* at 1-866-599-2267. The approved guideline will also be available on the CCNS website (www.cancercare.ns.ca).

The guideline will be reviewed three years after approval or revised before then as new evidence becomes available. The most recent version of this guideline will always be available on the CCNS website.

The development of this guideline was funded indirectly by CCNS via a stipend for the Hematology Cancer Site Team's operations. CCNS staff also support the guideline development process. CCNS directly funded the design, printing and dissemination of the guideline survey as well as the approved guideline. The views and interests of CCNS have not influenced the Hematology CST's recommendations in this guideline.

Summary of Reviewers for AML Guideline- By Profession and Province

Sent to Reviewers: By Specialty:	By Province:					Responses	
	NS	NB	PEI	NL	TOTALS	Number	Percent
Family Physician	1				1	0	0%
Internal Medicine	1				1	0	0%
Medical Oncology	3	2	2	2	9	1	11%
Nurse	3	5	1	2	11	5	45%
Pathology	10	7	1		18	1	6%
Pharmacist	25	10	3	11	49	4	8%
Radiation Oncology	3	9	1	1	14	0	0%
Hematologist	3	3		5	11	3	27%
TOTALS	49	36	8	21	114	14	No Answer = 6
Responses:							
Number Returned	9	2	0	4	15		
Percent Response	18%	6%	0%	19%	No Answer = 5		

Total Responses	20	18%
Response Rate (excluding Pharmacists)		25%

1 Is this guideline relevant to your practice?

Yes = 15 No = 4 N. A. = 1

2 A guideline on this topic will be useful to clinicians.

Strongly Agree =	4	Agrees	14
Agree =	10	Disagrees	1
Neither =	0	N. A.	5
Disagree =	1		
Strongly Disagree =	0		

3 You agree with the guideline.

Strongly Agree =	3	Agrees	11
Agree =	8	Disagrees	1
Neither =	3	N. A.	5
Disagree =	1		
Strongly Disagree =	0		

4 The format of the guideline is easy to use.

Strongly Agree =	4	Agrees	13
Agree =	9	Disagrees	0
Neither =	2	N. A.	5
Disagree =	0		
Strongly Disagree =	0		

6 Would you use this guideline in your own practice? Yes = 8

Comments:

* Decision aid when caring for an AML patient=4

* Better understanding about how AML is detected and managed=8

* Aid for patient education about AML = 6

No = 1 Unsure = 5 N. A. = 6
If NO or UNSURE

* You do not believe in guidelines as a decision aid=1

* You do not feel a practice guideline on this topic is required =1

* The recommended treatment practice is not practical in your setting =2

7 This guideline should be disseminated to all appropriate practitioners in Nova Scotia.

Yes = 12 N. A. = 6
No = 0 Unsure = 2

If NO or UNSURE

* The recommended treatment practice is not practical in your setting = 2

* The recommended treatment practice is unlikely to be accepted by your patient = 1

8 This guideline should be disseminated to all appropriate practitioners in Atlantic Canada.

Yes = 8 N. A. = 7
No = 2 Unsure = 3

If NO or UNSURE

* You do not feel a practice guideline on this topic is required = 1

* The recommended treatment practice is not practical in your setting = 1

* The recommended treatment practice is unlikely to be accepted by your patient = 1

* Other provinces have their own guideline development processes = 2

* Not the mandate of *Cancer Care Nova Scotia* to distribute guidelines outside NS = 1

10 How should CCNS guidelines be disseminated once they are approved?

* paper copy = 13

* Palm Pilot/PDA = 8

* Website = 14

* CME = 5



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