Jennifer Goy, MD, MSc, Tyler Smith, MD, MHSc, Stephen Nantel, MD, Yasser Abou Mourad, MD, Raewyn Broady, MBChB, Sujaatha Narayanan, MBBS, Monica Hudoba, MD, David Pi, MBBC, MBA

The clinical and diagnostic pathway for adults with acute leukemia in BC

An efficient triage, transfer, and workup process is critical when results from a blood test or bone marrow assessment indicate a patient may have acute leukemia.

ABSTRACT: Acute leukemia is characterized by aggressive proliferation of clonal blast cells in the bone marrow. The disease is a medical emergency and thus requires efficient triaging of patients and appropriate testing of blood and bone marrow samples using a streamlined clinical and diagnostic pathway. Key considerations include the patient’s clinical status, age, and comorbidities, as well as the resource capabilities of the medical centre where the patient first presents. Given the urgency and complexity of managing patients with newly diagnosed acute leukemia, clinicians and pathologists from throughout British Columbia have helped develop provincial guidelines for the initial management of patients presenting with symptoms of acute leukemia. This process includes immediate consultation with physicians at the Leukemia/Bone Marrow Transplant Program of BC at Vancouver General Hospital to establish patient acuity and appropriate treatment plans. The diagnosis of acute leukemia usually involves one of two common clinical scenarios: circulating blasts are identified in a complete blood count sample (Scenario A) or blasts are detected unexpectedly in bone marrow aspirate or biopsy material obtained during an investigation for pancytopenia or another cytopenia (Scenario B). Both scenarios require efficient communication between the local pathologist and pathologists at Vancouver General Hospital, and between the local clinician and Leukemia/Bone Marrow Transplant Program staff to ensure the patient is triaged appropriately and all diagnostic materials are transferred to Vancouver General Hospital. Patients with high-risk features of acute leukemia (e.g., blast count higher than 100 x 10^9/L, febrile neutropenia, hypotension, clinical or morphologic features of acute promyelocytic leukemia) require immediate transfer.

Acute leukemia refers to a category of blood cancers characterized by aggressive proliferation of clonal blast cells in the bone marrow and, occasionally, in

Dr Goy is a hematologist and clinical fellow in the Leukemia/Bone Marrow Transplant Program of BC. Dr Smith is a hematopathologist in the Division of Hematopathology at Vancouver General Hospital, and a clinical assistant professor at UBC. Dr Nantel is a hematologist and division head in the UBC Division of Hematology, and a clinical assistant professor at UBC. Dr Abou Mourad is a hematologist at the Leukemia/Bone Marrow Transplant Program of BC, and a clinical assistant professor at UBC. Dr Broady is a hematologist and director of the Leukemia/Bone Marrow Transplant Program of BC, and an associate professor at UBC. Dr Narayanan is a hematologist at the Leukemia/Bone Marrow Transplant Program of BC, and a clinical assistant professor at UBC. Dr Hudoba is a hematopathologist and division head of the Division of Hematopathology at Vancouver General Hospital, and a clinical assistant professor at UBC. Dr Pi is a hematopathologist at Vancouver General Hospital, and a clinical assistant professor at UBC.
the tissues. There are two main types of acute leukemia based on whether the malignant blast lineage is myeloid (acute myeloid leukemia or AML) or lymphoid (acute lymphoblastic leukemia or ALL). In contrast to the pediatric setting, where ALL predominates, AML is much more common in the adult setting and accounts for 90% of acute leukemia cases.1

Given the urgency and complexity of managing patients with newly diagnosed acute leukemia, clinicians and pathologists from throughout British Columbia have helped develop provincial guidelines for the initial management of patients presenting with symptoms of acute leukemia. In most cases, these patients will receive treatment through the Leukemia/Bone Marrow Transplant (L/BMT) Program of BC at Vancouver General Hospital (VGH).

**Initial management**

Acute leukemia poses a number of diagnostic and treatment challenges. Patient symptoms may be nonspecific in nature (e.g., fatigue, weight loss) and the complete blood count will often show one or more cytopenias. Frequently circulating blasts are present on the complete blood count but not in all cases. Further complicating matters, many patients with undiagnosed acute leukemia will first present with life-threatening complications, including febrile neutropenia, severe anemia, and major bleeding as a result of normal hematopoietic cells in the bone marrow being replaced by leukemic blasts. Patients with high numbers of circulating blasts can also develop severe pulmonary and central nervous system complications. Delays in the diagnosis and treatment of acute leukemia can be fatal.

**Workup when acute leukemia is suspected**

The acquisition of good-quality samples from bone marrow aspiration and trephine biopsy is critical when acute leukemia is suspected. The marrow aspirate is of particular importance because it is used for three key tests: (1) morphologic analysis to confirm that blasts account for at least 20% of bone marrow cells; (2) flow cytometry testing (immunophenotyping) to determine the leukemic blast phenotype; and (3) cytogenetic and molecular genetic testing to determine prognosis and guide overall therapy.

Acute promyelocytic leukemia (APL) is an important subtype of AML that requires immediate treatment. This subtype has a 10% mortality risk around the time of diagnosis due to excessive bleeding from enhanced fibrinolysis, but a far superior long-term survival rate (70% to 90%) over 5 years compared with most other acute leukemia subtypes.2

The leukemic cells in APL may have the characteristic bilobed nuclei and multiple Auer rods or so-called faggot cells (**Figure 1**). APL usually arises from translocation t(15;17) involving the retinoic acid receptor. Rapid initiation of all-trans retinoic acid (ATRA) therapy along with arsenic trioxide is associated with improved survival over both the short and long term. APL epitomizes the need for efficient recognition and treatment of acute leukemia.

**Leukemia/Bone Marrow Transplant Program of BC**

All adult patients receiving intensive induction chemotherapy for acute leukemia in British Columbia and Yukon are treated through a single specialized centre, the Leukemia/Bone Marrow Transplant Program of BC at Vancouver General Hospital (www.leukemiabmtprogram.com/index.html). This program operates a 31-bed inpatient ward at VGH, a day ward that accommodates 40 to 50 outpatient visits per day, and an outpatient clinic.

In addition to the 14 attending
physicians, the L/BMT program has a specialized team of caregivers that includes clinical fellows, GP oncologists, internists, registered nurses, nurse practitioners, clinical pharmacists, allied health professionals, administrative staff, and support staff. **Figure 2** shows the number of patients referred to the L/BMT program by each health authority from 2000 to 2014, while **Figure 3** shows the different malignancies identified in cases referred to the program from 2013 to 2014.

**Induction chemotherapy**

Patients with acute leukemia who are deemed eligible for curative-intent treatment receive a standardized induction chemotherapy regimen through the L/BMT program on an inpatient basis. This regimen is aimed at achieving remission so that consolidative chemotherapy and possibly stem cell transplantation can follow. Treatment outcomes have improved over time with advances in prognostic stratification, supportive care, and stem cell transplantation.

**Acuity categories**

Acute leukemia cases make up the majority of inpatient referrals to the L/BMT program but finite resources exist, particularly for inpatient beds. When the L/BMT attending physician receives a referral for a suspected case of acute leukemia, two critical assessments are made:

- Is the patient eligible for intensive induction chemotherapy?
- If the patient is eligible, is an urgent transfer to VGH required?

Using the clinical summary checklist shown in **Figure 4**, the patient is placed in one of three acuity and treatment eligibility categories.

**Category 1: High-risk patients with leukemia requiring immediate transfer to VGH**

Acute leukemia patients eligible for induction chemotherapy who present with high-risk features (e.g., blast count higher than 100 x 10⁹/L, CNS/respiratory symptoms, coagulopathy, suspected APL, hemodynamic instability) require life-or-limb-saving transfer (LLST) to Vancouver General Hospital even if they are deemed stable, since their clinical status can deteriorate in a matter of hours. Frequently these patients require emergency transfer to the VGH ICU. In addition, if APL is suspected the patient will need immediate preemptive initiation of ATRA to reduce the risk of bleeding and the need for aggressive transfusion support.

In the situations described above, where the diagnosis of acute leukemia is clear, it is generally preferable to delay the diagnostic bone marrow biopsy until the Category 1 patient arrives at VGH. This allows for the pretreatment diagnostic workup to be expedited at VGH and for results to be immediately available to L/BMT.

**Figure 2.** British Columbian patients referred to the Leukemia/Bone Marrow Transplant Program of BC, by health authority, 2000 to 2014.

**Figure 3.** Hematologic malignancy subtypes diagnosed in 1090 cases (Yukon cases not included) referred to the Leukemia/Bone Marrow Transplant Program of BC, 2013 to 2014.
The clinical and diagnostic pathway for adults with acute leukemia in BC

staff. Furthermore, this prevents delays caused by transfer of diagnostic materials and uncertainty regarding the adequacy of a bone marrow biopsy sample obtained at the referring site, and may allow the patient to avoid a repeat marrow biopsy.

**Category 2: Stable patients with leukemia requiring nonimmediate transfer to VGH**
The majority of acute leukemia referrals to the L/BMT program are Category 2 cases. In the absence of high-risk features, patients younger than 65 without major medical comorbidities are usually considered eligible for induction therapy, and patients 65 and older are less frequently eligible for aggressive induction. Medical comorbidities that would preclude the delivery of chemotherapy include, but are not limited to, significant cardiac or respiratory disease and significant hepatic or renal insufficiency. For Category 2 patients, the timing of transfer to VGH is determined by the L/BMT attending physician based on bed availability on the inpatient ward and the management resources in the referring hospital, particularly transfusion support. Category 2 patients are usually transferred from a community hospital to VGH within 48 to 72 hours. In small communities, platelets are not readily available, making the transfer of patients requiring platelet transfusions more urgent. As with Category 1 patients, it is preferable in the majority of cases to have the diagnostic bone marrow tests performed at VGH rather than the referring site.

**Category 3: Older patients with leukemia not likely to be eligible for induction chemotherapy at VGH**
Unfortunately, the treatment of acute leukemia in patients 65 and older remains extremely challenging. In addition to having higher rates of negative prognostic markers (i.e., complex karyotype) that render their disease more chemotherapy-resistant, older patients tolerate intensive induction regimens poorly. The impact on quality of life seen with intensive induction needs to be considered carefully in this population, where median survival is less than 1 year, even with intensive chemotherapy. Age, however, should not be the sole determinant when considering eligibility for treatment, since induction therapy may still prolong survival in select older patients with a favorable disease profile and no major comorbidities. The classic example is APL, where curative therapy may be attempted even in patients older than 80. Palliative chemotherapies such as hydroxyurea are available for symptom control and clinical trials are underway to investigate noncurative but potentially life-prolonging therapies. For these reasons, the decision to offer induction therapy to older patients (65 to 70 years of age) is made by L/BMT staff on a case-by-case basis. Only in very rare circumstances would a fit patient 70 and older be offered induction chemotherapy, as program data indicate the median survival of patients in this group is 6 months with intensive treatment and induction-related 30-day mortality is as high as 30%. Even if the referring physician is doubtful about the patient’s eligibility for induction therapy, consultation with the on-call L/BMT attending physician is recommended. L/BMT staff can determine if an older patient with AML is eligible for any open clinical trials at VGH and, more importantly, provide assistance with supportive care and communication with the patient and family.

**Diagnostic considerations**
The medical laboratory plays a crucial role in recognizing acute leukemia,
especially given the nonspecific clinical signs and symptoms patients often exhibit. Since the morphology of leukemic blasts can vary considerably among patients and across leukemic subtypes, identifying blasts can be challenging for medical laboratories in smaller centres that encounter leukemia infrequently. Delays in detecting acute leukemia can also result from poor-quality bone marrow samples. Two common problems are a narrow biopsy sample consisting mainly of cortical bone and a hemodilute marrow aspirate lacking marrow particles and consisting mainly of blood, although on occasion a "dry tap" can also be due to the patient’s marrow pathology. For these reasons, it is crucial that bone marrow samples be obtained by an experienced physician who performs the procedure regularly. Ideally, a trained laboratory technologist will be present at the bedside during marrow aspiration to make the slides with a fresh nonclotted sample and to confirm the presence of particles that are the hallmark of good-quality aspirate.

Usually the diagnosis of acute leukemia involves one of two scenarios:
- Identification of circulating blasts (or "other cells") in a complete blood count sample (Scenario A).
- Detection of increased blasts in a bone marrow aspirate or biopsy sample obtained for investigating pancytopenia or another cytopenia where acute leukemia is not necessarily suspected (Scenario B).

The clinical process followed in each of these scenarios is shown in Figure 5. For both scenarios, many of the same principles apply, including efficient communication between local and VGH pathologists and between local and L/BMT clinicians to ensure patients and their diagnostic materials are triaged appropriately.

### Scenario A: Acute leukemia probable based on peripheral blood findings

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Clinical process</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urgent AL</strong></td>
<td>Pathologist → alert MRP to call VGH BMT for urgent patient transfer to VGH</td>
</tr>
<tr>
<td>1. Suspected APL (bilobed/faggot cells)</td>
<td>Do NOT arrange local BMBx</td>
</tr>
<tr>
<td>2. Age ≤ 70 y</td>
<td>Local pathologist ↔ VGH HP communication</td>
</tr>
<tr>
<td>WBC &gt; 100</td>
<td>VGH BMT → page VGH HP on-call, urgent BMBx on arrival at VGH</td>
</tr>
<tr>
<td>3. Age ≤ 70 y unstable</td>
<td>Rapid FISH for t(15;17) if indicated</td>
</tr>
</tbody>
</table>

**AL, likely Tx at VGH**

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Clinical process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 70 y</td>
<td>Pathologist → alert MRP to call VGH BMT for possible patient transfer to VGH</td>
</tr>
<tr>
<td>2. Patient does not meet above criteria</td>
<td>If planned transfer to VGH, above measures should be taken</td>
</tr>
<tr>
<td></td>
<td>If no plan to transfer to VGH, BMBx at regional hub</td>
</tr>
</tbody>
</table>

**AL, unlikely Tx at VGH**

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Clinical process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 70 y</td>
<td>BMBx (transfer to regional hub if necessary, can skip if frail/elderly)</td>
</tr>
<tr>
<td>2. APL not suspected</td>
<td>VGH HP = consultation support</td>
</tr>
</tbody>
</table>

### Scenario B: Acute leukemia discovered following bone marrow assessment

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Clinical process</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urgent AL</strong></td>
<td>Pathologist → alert MRP to call VGH BMT for urgent patient transfer to VGH</td>
</tr>
<tr>
<td>1. Suspected APL (bilobed/faggot cells)</td>
<td>Local pathologist ↔ VGH HP communication</td>
</tr>
<tr>
<td>2. Age ≤ 70 y</td>
<td>Local pathologist → send BMBx slides (+/− flow PDFs) to VGH HP</td>
</tr>
<tr>
<td>3. Patient unstable</td>
<td>VGH BMT → page VGH HP on-call, determine if repeat BMBx necessary</td>
</tr>
<tr>
<td></td>
<td>Rapid FISH for t(15;17) if indicated</td>
</tr>
</tbody>
</table>

**AL, likely Tx at VGH**

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Clinical process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 70 y</td>
<td>Pathologist → alert MRP to call VGH BMT for possible patient transfer to VGH</td>
</tr>
<tr>
<td>2. Patient does not meet above criteria</td>
<td>If planned transfer to VGH, above measures should be taken</td>
</tr>
<tr>
<td></td>
<td>If no plan to transfer to VGH, BMT to determine whether BMBx workup to be performed at local hub or diagnostic materials sent to VGH</td>
</tr>
</tbody>
</table>

**AL, unlikely Tx at VGH**

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Clinical process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 70 y</td>
<td>Regional hub BMBx workup</td>
</tr>
<tr>
<td>2. Patient does not meet above criteria</td>
<td>VGH HP = consultation support</td>
</tr>
</tbody>
</table>

**Figure 5.** Clinical process for two scenarios in the diagnosis of acute leukemia.
L/BMT inpatient ward. For lower acuity cases in remote hospitals, it may be appropriate to obtain bone marrow samples and provide initial supportive management at a regional centre in the health authority.

Unfortunately, patients arriving at VGH for treatment may need to undergo repeat diagnostic bone marrow biopsies. This can occur if treating physicians have not yet reviewed material or samples obtained elsewhere have not yet arrived at VGH.

For patients who will be treated at VGH (i.e., Category 1 and 2 patients) there are several advantages to having the diagnostic bone marrow samples obtained at VGH. Being the provincial referral centre for acute leukemia, VGH has a streamlined diagnostic process that can be carried out on weekends when clinically necessary. The specialized laboratory technologists are experienced in dealing with common challenges encountered in obtaining and preparing diagnostic materials, and can ensure these materials are sent to the appropriate laboratories for flow cytometry, cytogenetic, and molecular genetic analyses. In addition, if the marrow aspiration and biopsy are performed at VGH, the results are more easily accessed by the treating L/BMT staff and patients have the opportunity to provide bone marrow samples for research. Finally, when additional bone marrow samples are obtained following treatment to compare blast morphology and better assess remission status, it is easier if the initial diagnostic slides were prepared and stained in the same manner as posttreatment slides and are readily available on site.

**Scenario B: Acute leukemia discovered following bone marrow assessment**

When leukemia is identified in a patient who has undergone a bone marrow biopsy in the workup for pancytopenia or another cytopenia, the clinical process is somewhat different, but efficient communication is just as critical. For most cases, there should be immediate communication between local and VGH pathologists, between the local pathologist and local clinician, and between the local clinician and L/BMT staff. In addition, the VGH hematopathologist and L/BMT staff should be informed of high acuity cases, particularly if APL is suspected, as the VGH cytogenetics laboratory has a procedure for rapid analysis for t(15;17). In cases where the diagnosing pathologist is unable to reach the local clinician responsible for the patient’s care, the authors feel it is the pathologist’s responsibility to contact the patient directly with instructions to proceed to the nearest hospital emergency room, as acute leukemia is a medical emergency.

If a patient will likely be treated at VGH, it is critical to send any diagnostic bone marrow materials to VGH on an urgent basis so the hematopathologist can determine if a repeat bone marrow assessment is needed before treatment begins. It is also important to ensure that marrow aspirate samples have been sent to the appropriate flow cytometry, cytogenetics, and molecular genetics laboratories, as this provides critical ancillary diagnostic and prognostic information required by the treating L/BMT clinician. Often, patients referred with acute leukemia to VGH have to undergo a repeat bone marrow assessment when the diagnostic slides from the referring centre do not arrive in a timely manner or have not been sent for the appropriate adjunctive testing. Once treatment has been initiated it is generally not possible to obtain useful samples.

**Clinical and diagnostic pathway**

The pathway for triage, transfer, and workup for suspected acute leukemia is summarized in Figure 6. Patients often present with circulating blasts, which may be reported as “immature cells” or “other cells” on the complete blood count differential.

Suspected adult cases of acute leukemia should be discussed immediately with the on-call L/BMT attending physician, while suspected pediatric cases (patients younger than 17) should be referred immediately to the BC Children’s Hospital on-call oncology service.

The referring physician for an adult patient should provide the L/BMT attending physician with the clinical information required to determine whether an urgent life-or-limb-saving transfer is needed. All patients with suspected acute leukemia who will be transferred to the L/BMT program for induction therapy (i.e., Category 1 and 2 patients) should have their diagnos-
tic bone marrow assessment completed at Vancouver General Hospital and not at the referring hospital. Patients who are not candidates for intensive induction therapy should have their diagnostic bone marrow assessment completed at the referring site, but only after discussion with the L/BMT attending physician.

**Summary**

Any case where acute leukemia is probable should be regarded as a medical emergency. In BC, a streamlined clinical and diagnostic pathway facilitates efficient triaging and appropriate testing of blood and bone marrow samples. When a patient older than 17 presents with clinical features of acute leukemia, the most responsible physician should immediately contact the attending physician at the Leukemia/Bone Marrow Transplant Program at Vancouver General Hospital to discuss the possibility and timing of transfer and where the bone marrow assessment should be performed.

**Competing interests**

None declared.

**References**


**Figure 6. Acute leukemia clinical and diagnostic pathway.**

**Abbreviations**

BCCH = BC Children’s Hospital  
BCPTN = BC Patient Transfer Network  
FISH = fluorescent in situ hybridization  
L/BMT = Leukemia/Bone Marrow Transplant Program  
LLST = life-or-limb-saving transfer  
MRP = most responsible physician  
VGH = Vancouver General Hospital