



**PRINCESS MARGARET CANCER CENTRE**  
**CLINICAL PRACTICE GUIDELINES**

**LEUKEMIA SITE GROUP**

ACUTE LYMPHOBLASTIC LEUKEMIA

# Leukemia Site Group – Acute Lymphoblastic Leukemia

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## 1. Introduction

These guidelines relate to the management of acute lymphoblastic leukemia (ALL) as currently practiced at Princess Margaret Cancer Centre (PM). This document considers both B-ALL and T-ALL.

## 2. Prevention

Preventive strategies are generally not available for ALL.

## 3. Screening and Early Detection

Screening and Early Detection is generally not relevant in ALL.

## 4. Diagnosis

The comprehensive diagnosis of ALL is based on the examination of the peripheral blood and bone marrow both morphologically and by flow-cytometry +/- immunocyto- and immunohistochemical studies, as appropriate, and by additional cytogenetic and molecular studies, ideally performed on the bone marrow.

In cases in which bone marrow aspiration yields an adequate sample, additional bone marrow biopsy, while complementary, is not essential for diagnosis. In cases in which the aspirate is unsuccessful or inadequate, however, biopsy is essential.

## 5. Pathology

Hematopathology (including flow cytometry), cytogenetics, and molecular studies contribute to the comprehensive diagnosis of ALL.

### 5i. Hematopathology

The **French-American-British (FAB) classification** (1979) was based on morphology and immunophenotyping.

**Table 1. FAB Classification of ALL**

FAB subtype	Name
L1	Small uniform cells; more mature-appearing lymphoblasts
L2	Large varied cells; more immature and pleomorphic
L3	Large varied cells with vacuoles (Burkitt-like); blasts with cytoplasmic vacuolizations and surface expression of immunoglobulin, and the bone marrow often has an appearance described as a <i>starry sky</i> owing to the presence of numerous apoptotic cells; associated with a variety of translocations that involve translocation of the <i>c-myc</i> proto-oncogene to the immunoglobulin gene locus t(2;8), t(8;12), and t(8;22)

Each subtype was then further classified by immunophenotyping into pre-B cell and pre-T cell ALL. Mature B-cell ALL (L3) is now classified as Burkitt lymphoma/leukemia.

However, as the morphological FAB classification had little clinical or prognostic relevance, it has been supplanted by the **World Health Organization (WHO) classification** (2001, 2008, 2016) which is based on immunophenotyping plus cytogenetics. Burkitt's leukemia/lymphoma (Former FAB L3) and the provisional entity Burkitt-like lymphoma with 11q aberration are classified as a mature B cell neoplasms.

**Table 2. WHO classification of Myeloid Neoplasms and Acute Leukemia (2016)**

<b>AML and related neoplasms</b>	<b>Entities</b>
AML with recurrent genetic abnormalities	<ul style="list-style-type: none"> <li>• AML with t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i></li> <li>• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i></li> <li>• APL with <i>PML-RARA</i></li> <li>• AML with t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i></li> <li>• AML with t(6;9)(p23;q34.1); <i>DEK-NUP214</i></li> <li>• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM</i></li> <li>• AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); <i>RBM15-MKLI</i></li> <li>• Provisional entity: AML with <i>BCR-ABL1</i></li> <li>• AML with mutated <i>NPM1</i></li> <li>• AML with biallelic mutations of <i>CEBPA</i></li> <li>• Provisional entity: AML with mutated <i>RUNX1</i></li> </ul>
AML with myelodysplasia-related changes	
Therapy-related myeloid neoplasms	
AML, Not Otherwise Specified (NOS)	<ul style="list-style-type: none"> <li>• AML with minimal differentiation</li> <li>• AML without maturation</li> <li>• AML with maturation</li> <li>• Acute myelomonocytic leukemia</li> <li>• Acute monoblastic/monocytic leukemia</li> <li>• Pure erythroid leukemia</li> <li>• Acute megakaryoblastic leukemia</li> <li>• Acute basophilic leukemia</li> <li>• Acute panmyelosis with myelofibrosis</li> </ul>
Myeloid Sarcoma	
Myeloid proliferations related to Down syndrome	<ul style="list-style-type: none"> <li>• Transient abnormal myelopoiesis (TAM)</li> <li>• Myeloid leukemia associated with Down syndrome</li> </ul>
<b>Blastic plasmacytoid dendritic cell neoplasm (BPDCN)</b>	
<b>Acute leukemias of ambiguous lineage</b>	<ul style="list-style-type: none"> <li>• Acute undifferentiated leukemia</li> <li>• Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i></li> </ul>

	<ul style="list-style-type: none"> <li>• MPAL with t(v;11q23.3); <i>KMT2A</i> rearranged</li> <li>• MPAL, B/myeloid, NOS</li> <li>• MPAL, T/myeloid, NOS</li> </ul>
<b>B-lymphoblastic leukemia/lymphoma</b>	<ul style="list-style-type: none"> <li>• B-lymphoblastic leukemia/lymphoma, NOS</li> <li>• B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities</li> <li>• B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i></li> <li>• B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); <i>KMT2A</i> rearranged</li> <li>• B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); <i>ETV6-RUNX1</i></li> <li>• B-lymphoblastic leukemia/lymphoma with hyperdiploidy</li> <li>• B-lymphoblastic leukemia/lymphoma with hypodiploidy</li> <li>• B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) <i>IL3-IGH</i></li> <li>• B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); <i>TCF3-PBX1</i></li> <li>• <i>Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like</i></li> <li>• <i>Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21</i></li> </ul>
<b>T-lymphoblastic leukemia/lymphoma</b>	<ul style="list-style-type: none"> <li>• <i>Provisional entity: Early T-cell precursor lymphoblastic leukemia</i></li> </ul>
<i>Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma</i>	

### Immunophenotype:

ALL can be broadly classified into 3 groups based on immunophenotype: precursor B-cell ALL, mature B-cell ALL and T-cell ALL.

**Table 3. Immunophenotype in ALL**

Subgroup	Frequency	Immunophenotype
Early precursor B-cell ALL	70-80%	Tdt, CD19, CD22 and CD79a expression; absence of CD10 expression
Precursor B-cell ALL		cIg, CD10, Tdt, CD19, CD22 and CD79a expression
Mature B-cell ALL (FAB ALL L3; Burkitt leukemia)	≤ 5%	sIg, clonal lambda or kappa light chain, CD10, CD19, CD20 and CD22 expression; absence of Tdt expression
T-cell ALL	10-25%	Tdt and sCD3 or cCD3 expression;

		variable expression CD1a, CD2, CD5, CD7 and CD52
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Up to 60% of patients with Philadelphia-like ALL will overexpress cytokine receptor-like factor 2/thymic stromal lymphopoietin receptor (*CRLF2/TSLPR*).

### 5ii. Cytogenetics

The cytogenetics of adult ALL is considerably less complex than is that of pediatric ALL or that of adult AML.

**Table 4. ALL Cytogenetic Risk Group (SWOG and MRC)<sup>a</sup>**

Risk Status	SWOG coding		MRC coding	
	N=140		N=782	
Standard/ Favorable	High hyperdiploidy (51-65 chr) & no structural changes	N=1 (0.1%) <i>OS</i> <sub>5y</sub> 50%	High hyperdiploidy (51-65 chr); del9p	N=148 (19%) <i>OS</i> <sub>5y</sub> 50%
Intermediate	Normal; 11q abn (not <i>MLL</i> ); del6q; del17p; del9p; del12p; -13/del13q; t(14q32); t(10;14); Low hyperdiploidy (47-50 chr); other TCR translocations; tetraploidy (>80) & no structural changes; All others	N=72 (51%) <i>OS</i> <sub>5y</sub> 40-50%		
High	-7; del17p; +8; other 11q23/ <i>MLL</i> translocations; t(1;19) or t(17;19), t(5;14)/ <i>TLX3</i> or <i>CALM-AF10</i> in T-ALL	N=12 (8%) <i>OS</i> <sub>5y</sub> 30-40%		
Very High	t(4;11)/ <i>AF4-MLL</i> +; t(8;14)/ <i>MYC-IGH</i> ; complex cyto (> 5 abn) & no translocations & low hypodiploidy (30-39 chr)/near triploidy (60-78 chr)	N=19 (14%) <i>OS</i> <sub>5y</sub> ≤ 30%	t(4;11)(q21;q23); t(8;14); complex cyto (> 5 abn); Low hypodiploidy(30-39 chr)/near triploidy (60-78 chr)	N=142 (18%) <i>OS</i> <sub>5y</sub> ≤ 30%

<sup>a</sup> Philadelphia-negative B-cell ALL (predates description of Philadelphia-like B-cell ALL)

The key treatment-changing considerations in adult ALL are the presence of the Philadelphia chromosome [t(9;22(q34;q11)], translocations involving *MLL* [the

prognostic import of t(4;11) in adults remains controversial], or *myc*, and hypodiploidy (most important in pediatric cases).

The Philadelphia-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2* or *PDGFRB* and mutations involving *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3* and *JAK2* (in combination with *CRLF2* gene fusions).

### 5iii. Molecular

Molecular testing at the time of diagnosis in ALL, is generally restricted to determining Ph chromosome (*bcr-abl*) positivity and *MLL* rearrangement.

Ph+ve status features prominently in decisions regarding allogeneic stem cell transplantation (alloSCT). Ph+ve molecular testing also plays an important role in ongoing, post-remission, minimal residual disease (MRD) assessment (see sections 6. and 8. below). Prospective monitoring of MRD has the potential to identify patients at risk of relapse. The best frequency for molecular assessment and the best source of cells for testing (blood or marrow) is unclear; however, at the current time, molecular analyses are usually performed every 3 months.

## 6. Management

### 6.1 Management Algorithms

Based on an assessment of prognostic factors (see Table 5 below), an individualized treatment plan is chosen.

**Table 5, Prognostic Factors in ALL (B and T-cell)**

	Variable
Poor risk	<ul style="list-style-type: none"> <li>• Age &gt; 35 years (i.e. not adolescent and young adult)</li> <li>• WBC &gt; 30 x 10<sup>9</sup>/L (for B-cell ALL)</li> <li>• WBC &gt; 100 x 10<sup>9</sup>/L (for T-cell ALL)</li> <li>• Greater than 4 weeks to CR</li> <li>• Philadelphia-positive (<i>bcr-abl</i>; t(9;22) in 30% adults)</li> <li>• Philadelphia-like</li> <li>• Translocations involving <i>MLL</i> and/or <i>myc</i></li> <li>• Hypodiploidy (mostly pediatric patients)</li> </ul>

Chemotherapy protocols for newly diagnosed patients above and below age 60 are listed in section 6.2.1 below.

Stem cell transplant (SCT) indications are found in section 6.4 below.

Chemotherapeutic approaches to relapsed/refractory disease are found in section 6.2.2 below.

## **6.2 Treatment Regimens**

Newly diagnosed patients are considered in section 6.2.1. Patients with non-responding and relapsed/refractory disease are considered in section 6.2.2.

### **6.2.1 Newly Diagnosed Patients**

Induction chemotherapy is defined primarily by age, by cytogenetics, and by clinical presentation (e.g. mediastinal mass with actual or impending SVC or airway obstruction). Prophylactic CNS therapy is included routinely.

Adolescent and young adults with ALL have improved outcomes when treated with a pediatric or pediatric-like regimen.

The PM Dana Farber Cancer Institute (DFCI)-based protocol (and its variants), is preferred for initial therapy, and overall outcomes are better. However, in the situation of a large mediastinal mass, it may be preferable to use HyperCVAD up-front, due to the early cyclophosphamide component. In such a case, it would be reasonable to switch over to the DFCI CNS phase, after completing HyperCVAD parts 1A and 1B.

#### **6.2.1.1-4 PM DFCI-based protocols:**

The DFCI protocols are defined by Ph status and by age. At the current time, Ph-like ALL are treated with the same induction treatment protocols as Ph-negative ALL.

##### **6.2.1.1 DFCI protocol < age 60, Ph-ve**

#### **Induction Phase (29 days)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) D1, 8, 15, & 22  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1 & 2  
Methotrexate (MTX) 4 g/m<sup>2</sup>/d IV D3  
Leucovorin 200 mg/m<sup>2</sup> IV at 36h after start of MTX, then 24 mg/m<sup>2</sup> IV q6h until [MTX < 0.1 uM]  
L'asparaginase 25,000 U/m<sup>2</sup> IM D5  
Prednisone 10 mg/m<sup>2</sup> po qid **or** methylprednisolone 8 mg/m<sup>2</sup> IV qid D1-29  
**Ara-C 70 mg IT D1**  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D15 & 29**

#### **CNS Phase (21 days)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) D1  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days (D1-14)  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D1, 4, 8 & 11**



### **Intensification Phase (30 weeks; ten 3-week cycles)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) week 1 (D1)  
Doxorubicin 30 mg/m<sup>2</sup> IV (LVEF ≥ 50%) week 1 (D1) for cycles 1-7 *then*  
MTX 30 mg/m<sup>2</sup> IV or IM 24h post-MTX for cycles 8-10  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 9 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
L'asparaginase 12,500 U/m<sup>2</sup> IM weeks 1, 2, & 3  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT cycles 6 & 9**

### **Continuation Phase (72 weeks; twenty-four 3-week cycles)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) week 1 (D1)  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 6 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
Methotrexate 30 mg/m<sup>2</sup> IV or IM on weeks 1, 2, & 3  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT cycles 2, 8, 14 & 20**

### **Other Supportive Measures**

Allopurinol 300 mg po daily x 7 days (induction; D1-7)  
NaHCO<sub>3</sub> (induction)  
Fluconazole 400 mg po daily (induction; start D3)  
Septra SS 2 tabs po qM, W & F  
Bisphosphonates, calcium, and vitamin D  
Enoxaparin sc daily (weight adjusted during intensification)  
Bone mineral density & MRI hips and knees (end of intensification)  
Baseline MUGA scan

### **6.2.1.2 DFCI protocol < age 60, Ph+ve**

#### **Induction Phase (31 days)**

Imatinib 400 mg po daily x 16 days (D-2 to D14)  
Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) D1 & 8  
Vinblastine 10 mg IV D15  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1 & 2  
Methotrexate (MTX) 4 g/m<sup>2</sup>/d IV D3  
Leucovorin 200 mg/m<sup>2</sup> IV at 36h after start of MTX, then 24 mg/m<sup>2</sup> IV q6h until [MTX < 0.1 uM]  
Prednisone 10 mg/m<sup>2</sup> po qid **or** methylprednisolone 8 mg/m<sup>2</sup> IV qid D1-29  
**Ara-C 70 mg IT D1**  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D15 & 29**

### **CNS Phase (21 days)**

Imatinib 400 mg po daily x 21 days (D1-21)  
Vinblastine 10 mg IV D1  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days (D1-14)  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D1, 4, 8 & 11**

### **Intensification Phase (21 weeks; seven 3-week cycles)**

Imatinib 400 mg po daily x 21 days (D1-21)  
Vinblastine 10 mg IV week 1 (D1)  
Doxorubicin 30 mg/m<sup>2</sup> IV (LVEF ≥ 50%) week 1 (D1)  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 9 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT cycle 6**

### **Continuation Phase (72 weeks; twenty-four 3-week cycles)**

Imatinib 400 mg po daily x 21 days (D1-21)  
Vinblastine 10 mg IV week 1 (D1)  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 6 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
Methotrexate 30 mg/m<sup>2</sup> IV or IM on weeks 1, 2 & 3  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT cycles 5, 11, 17 & 23**

### **Other Supportive Measures**

Allopurinol 300 mg po daily x 7 days (induction; D1-7)  
NaHCO<sub>3</sub> (induction)  
Fluconazole 400 mg po daily (induction; start D5)  
Septra SS 2 tabs po qM, W & F  
Bisphosphonates, calcium, and vitamin D  
Bone mineral density & MRI hips and knees (end of intensification)  
Baseline MUGA scan

### **6.2.1.3 DFCI protocol ≥ age 60, Ph-ve**

**Induction Phase (28 days)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) D1, 8 & 15  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) **or** D1 & 2  
Methotrexate (MTX) 40 mg/m<sup>2</sup> IV D3  
Leucovorin 15 mg IV q6h x 4 starting 24 h post MTX  
L'asparaginase 12,000 U/m<sup>2</sup> IM D4  
Dexamethasone 40 mg po/IV daily D1-4 & 9-12  
**Ara-C 70 mg IT D1**  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D15**

**CNS Phase (21 days)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) D1  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days (D1-14)  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D1, 4, 8 & 11**

**Intensification Phase (21 weeks; seven 3-week cycles)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) week 1 (D1)  
Doxorubicin 30 mg/m<sup>2</sup> IV (LVEF ≥ 50%) week 1 (D1) for cycles 1-7  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 9 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
L'asparaginase 6000 U/m<sup>2</sup> IM weeks 1, 2 & 3  
**MTX 12 mg/Ara-C 40 mg/ hydrocortisone 15 mg IT cycle 6**

**Continuation Phase (72 weeks; twenty-four 3-week cycles)**

Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) week 1 (D1)  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 6 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
Methotrexate 30 mg/m<sup>2</sup> po on weeks 1, 2 & 3  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT cycles 5, 11, 17 & 23**

**Other Supportive Measures**

Allopurinol 300 mg po daily x 7 days (induction; D1-7)  
NaHCO<sub>3</sub> (induction)  
Fluconazole 400 mg po daily (induction; start D3)  
Septra SS 2 tabs po qM, W & F  
Bisphosphonates, calcium, and vitamin D  
Enoxaparin sc daily (weight adjusted during intensification)  
Bone mineral density & MRI hips and knees (end of intensification)  
Baseline MUGA scan

#### 6.2.1.4 DFCI protocol ≥ age 60, Ph+ve

##### **Induction Phase (31 days)**

Imatinib 400 mg po daily x 16 days (D-2 to D14)  
Vincristine 2 mg IV **or** vinblastine 10 mg IV (neuropathy) D1 & 8  
Vinblastine 10 mg IV D15  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1 & 2  
Methotrexate (MTX) 4 g/m<sup>2</sup>/d IV D3  
Leucovorin 200 mg/m<sup>2</sup> IV at 36h after start of MTX, then 24 mg/m<sup>2</sup> IV q6h until [MTX < 0.1 uM]  
Methylprednisolone 210 mg IV D1-4 & 9-12  
**Ara-C 70 mg IT D1**  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D15**

##### **CNS Phase (21 days)**

Imatinib 400 mg po daily x 21 days (D1-21)  
Vinblastine 10 mg IV D1  
Doxorubicin 30 mg/m<sup>2</sup>/d IV (LVEF ≥ 50%) D1  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days (D1-14)  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT D1, 4, 8 & 11**

##### **Intensification Phase (21 weeks; seven 3-week cycles)**

Imatinib 400 mg po daily x 21 days (D1-21)  
Vinblastine 10 mg IV week 1 (D1)  
Doxorubicin 30 mg/m<sup>2</sup> IV (LVEF ≥ 50%) week 1 (D1)  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Dexamethasone 6 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)  
**MTX 12 mg/Ara-C 40 mg/hydrocortisone 15 mg IT cycle 6**

##### **Continuation Phase (72 weeks; twenty-four 3-week cycles)**

Imatinib 400 mg po daily x 21 days (D1-21)  
Vinblastine 10 mg IV week 1 (D1)  
6-mercaptopurine 50 mg/m<sup>2</sup>/d po x 14 days starting week 1 (D1-14)  
Methotrexate 30 mg/m<sup>2</sup> po on weeks 1, 2 & 3  
Dexamethasone 6 mg/m<sup>2</sup> po bid x 5 days starting week 1 (D1-5)

### **Other Supportive Measures**

Allopurinol 300 mg po daily x 7 days (induction; D1-7)  
NaHCO<sub>3</sub> (induction)  
Fluconazole 400 mg po daily (induction; start D5)  
Septra SS 2 tabs po qM, W & F  
Bisphosphonates, calcium, and vitamin D  
Bone mineral density & MRI hips and knees (end of intensification)  
Baseline MUGA scan

### **6.2.1.5 HyperCVAD**

#### Patient Eligibility:

- ALL, relapsed after, or refractory to, DFCI induction therapy
- ALL in which DFCI regimen is contraindicated
- T-ALL with large mediastinal mass\*

\* in this circumstance, the mediastinal mass should be associated with known or impending SVC or airway obstruction. In this situation, it may be preferable to use HyperCVAD up-front, due to the early cyclophosphamide component. In such a case, it would be reasonable to switch over to the DFCI CNS phase, after completing HyperCVAD parts 1A and 1B.

#### Part A

- Cyclophosphamide 300 mg/m<sup>2</sup> over 3h IV Q12h x 6 doses (3 days; total 1800mg/m<sup>2</sup>)
- Doxorubicin 50 mg/m<sup>2</sup> IV on Day 4 (12 h after last dose of cyclophosphamide)
- Vincristine 2 mg IV on Day 4 (with daunorubicin) and Day 11
- Asparaginase 25,000 U/m<sup>2</sup> (max. 50,000 U) IM on Day 5
- Dexamethasone 40 mg PO/IV daily on Days 1-4 and 11-14
- CNS prophylaxis\*: Methotrexate 12 mg IT Day 2 & Ara-C 70 mg IT Day 11

#### Part B

- Methotrexate 1 g/m<sup>2</sup> IV over 24h on Day 1 (given with leucovorin rescue) or 40 mg/m<sup>2</sup> if edema or effusions present
- Ara-C 3 g/m<sup>2</sup> IV over 2 hours Q12h x 4 doses, on Days 2 and 3 (for patients age > 60 years use Ara-C 1.5 g/m<sup>2</sup>)

Repeat Parts A and B x 4 cycles at Q3 week intervals, or when recovery occurs.

Each subsequent cycle to start when:

1. there is recovery of mucosal function
2. the granulocyte count is > 0.5 x 10<sup>9</sup>/L
3. the platelet count is > 100 x 10<sup>9</sup>/L

N.B.: the goal is to give the treatment as rapidly as possible. If there are delays in treatment due to prolonged neutropenia, G-CSF may be added for subsequent cycles at a dose of 300 ug/d, starting on Day 11 and continuing until neutrophil count is > 2.0.

Stop G-CSF for at least one day before starting next cycle.

Bone marrow aspiration at the completion of cycle 1B. Continue therapy if CR achieved.  
\*If CSF positive, give IT chemo 2x weekly, alternating MTX and Ara-C, until CSF clear.

## **6.2.2 Recurrent/Persistent Disease**

### **6.2.2.1 HyperCVAD**

DFCI failures generally proceed to Hyper-CVAD (see Section 6.2.1.5)

### **6.2.2.2 FLAG-Ida**

#### Induction Regimen:

- Filgrastim (G-CSF) 300 mcg sc daily x 6 days (Days 0-5)
- Idarubicin 10 mg/m<sup>2</sup> IV push daily x 3 days (Days 1-3) (for LVEF ≥ 50%)
- Fludarabine 30 mg/m<sup>2</sup> IV daily x 5 days (Days 1-5)
- Cytarabine 2 g/m<sup>2</sup> IV daily over 4 hours x 5 days (Days 1-5) (to start 4 hours after the start of fludarabine)

#### Consolidation Regimen (Cycles 1 & 2):

- Filgrastim (G-CSF) 300 mcg sc daily x 4 days (Days 1-4)
- Idarubicin 10 mg/m<sup>2</sup> IV push daily x 2 days (Days 1 & 2) (for LVEF ≥ 50%)
- Fludarabine 30 mg/m<sup>2</sup> IV daily x 4 days (Days 1-4)
- Cytarabine 2 g/m<sup>2</sup> IV daily over 4 hours x 4 days (Days 1-4) (to start 4 hours after the start of fludarabine)

### **6.2.2.3 Blinatumomab**

Health Canada has approved blinatumomab for the treatment of adults with Ph-negative relapsed or refractory B-ALL. Blinatumomab is a bispecific CD19-directed CD3 T-cell engager (BiTE<sup>®</sup>) antibody construct product.

#### First Induction Regimen (Cycle 1) (4 weeks on, 2 weeks off):

- Each cycle is 6 weeks
- CSF prophylaxis with methotrexate 12 mg/cytarabine 40 mg/hydrocortisone 15 mg IT
- Blinatumomab 9 mcg/day IV continuous infusion on Days 1-7 then 28 mcg/day IV continuous infusion on Days 8-28

#### Second Induction Regimen or Consolidations (Cycles 2-5) (4 weeks on, 2 weeks off):

- Each cycle is 6 weeks
- CSF prophylaxis with methotrexate 12 mg/cytarabine 40 mg/hydrocortisone 15 mg IT
- Blinatumomab 28 mcg/day IV continuous infusion on Days 1-28

### Supportive Care:

- Cytokine release syndrome (CRS) –  
Infusion reactions are common and may not be distinguishable from CRS. Mild symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by tachycardia and hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure. Hemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported in the setting of CRS. Median time to onset of CRS is 2 days (and usually during first cycle of therapy). Risk factors for CRS include disease burden and initial starting dose of blinatumomab. In general, signs and symptoms of CRS are limited to the first cycle of the drug. CRS prophylaxis with dexamethasone is performed on day 1 and with dose escalation.
- Neurologic events –  
Neurologic events (any grade) were observed in approximately 50% of adult patients receiving blinatumomab. The median time to onset of neurologic symptom is within first 2 weeks of therapy and is generally reversible. Severe events, which may be fatal, include encephalopathy, seizures, speech disorder, cognitive disturbances, coordination and balance disorders.

### Management of CRS and neurologic events:

- Dexamethasone 8 mg IV push q8h for 3 days, then 8 mg IV push q12h for 2 days, then 8 mg IV push daily for 1 day, then 4 mg IV push daily for 1 day
- Rate of blinatumomab infusion may be reduced; however, in the event of Grade  $\geq 3$  neurologic events, blinatumomab should be stopped immediately. If the event has decreased to at least Grade 1 within a week, treatment may be restarted within 2 weeks (usually at 9 mcg/day IV continuous infusion and re-escalated as tolerated), but not earlier than 72 hours after the infusion was stopped.

### **6.2.2.4 Inotuzumab ozogamicin**

Inotuzumab ozogamicin is Health Canada approved as a monotherapy for the treatment of adults with relapsed or refractory CD22-positive Philadelphia chromosome (Ph)-positive and Ph-negative B-cell precursor ALL. Inotuzumab ozogamicin consists of the humanized monoclonal antibody against CD22, linked to a cytotoxic agent from the class of calicheamicins called ozogamicin.

To minimize risk of developing veno-occlusive disease (see below), treatment should be limited to 2 cycles of inotuzumab, for those patients proceeding to SCT.

For patients not proceeding to SCT who achieve CR/CRi and MRD negativity, treatment may be continued for a maximum of 6 total cycles.

### First Induction Regimen (Cycle 1):

- First cycle is 21 days
- Inotuzumab ozogamicin 0.8 mg/m<sup>2</sup> IV on Day 1 followed by inotuzumab ozogamicin 0.5 mg/m<sup>2</sup> IV on Days 8 & 15 [total dose per cycle = 1.8 mg/m<sup>2</sup>]

Re-induction (if not in CR/CRi after First Induction) Regimen:

- Cycle is 28 days
- Inotuzumab ozogamicin 0.8 mg/m<sup>2</sup> IV on Day 1 followed by 0.5 mg/m<sup>2</sup> IV on Days 8 & 15 [total dose per cycle = 1.8 mg/m<sup>2</sup>]

Consolidation Regimen (Cycles 2 or 3-6):

- Cycle is 28 days
- Inotuzumab ozogamicin 0.5 mg/m<sup>2</sup> IV on Days 1, 8 & 15 [total dose per cycle = 1.5 mg/m<sup>2</sup>]

Supportive Care:

- Veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome (SOS) – Hepatic SOS (aka hepatic VOD), is characterized by hepatomegaly, right upper quadrant pain, jaundice, and ascites. The disease resembles the Budd-Chiari syndrome clinically; however, hepatic venous outflow obstruction in SOS is due to occlusion of the terminal hepatic venules and hepatic sinusoids rather than the hepatic veins and inferior vena cava. Hepatic SOS typically occurs in the context of SCT, but may occur after other treatments (e.g. monoclonal antibodies conjugated with calicheamicin).

Veno-occlusive disease (VOD)/SOS is more frequent with inotuzumab ozogamicin therapy compared with standard of care regimens (23 of 164 [14.0%] vs 3 of 143 [2.1%]). VOD occurred in 3% of patients who did not proceed to transplant and 22% of patients who did proceed to transplant. In multivariate analysis, factors associated with increased VOD/SOS risk after HSCT in inotuzumab ozogamicin-treated patients were conditioning regimens containing dual alkylators, bilirubin levels at or above the upper limit of normal range at the last measurement before conditioning therapy or at the last measurement before follow-up SCT and prior SCT. In the univariate analysis, an age ≥55 years and the number of treatment cycles received were also identified as risk factors but did not remain significant in the multivariate analysis.

Management of VOD:

- Symptomatic management, including careful attention to fluid balance
- Continue to receive ursodiol prophylactically
- Defibrotide sodium is Health Canada approved for the treatment of adult and pediatric patients with hepatic VOD/SOS, with renal or pulmonary dysfunction following SCT therapy and has been used in this scenario for patients who received inotuzumab ozogamicin and developed VOD/SOS after SCT. However, its role/benefit in patients who develop VOD/SOS after inotuzumab ozogamicin in the absence of SCT is unclear.

**6.2.2.5 CD19 CAR T cell therapy**



Health Canada has approved tisagenlecleucel for use in pediatric and young adult patients 3 to 25 years of age with CD19-positive B-cell ALL who are refractory, have relapsed after allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse.

#### Supportive Care:

- Cytokine release syndrome (CRS) – Symptoms include fever, malaise, anorexia and myalgias. CRS can affect any organ in the body, including cardiovascular, respiratory, gastrointestinal, hepatic, renal, hematologic (including coagulopathy), integumentary and neurological. Potential life-threatening complications include capillary leak syndrome with pulmonary compromise, adult respiratory distress syndrome (ARDS), hypotension, cardiac dysfunction, arrhythmias, renal and/or hepatic failure, disseminated intravascular coagulation, symptoms similar to macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), tumor lysis syndrome, encephalopathy and cerebral edema. Timing of symptom onset and CRS severity depends on the agent and the magnitude of immune cell activation.

#### Management of CRS:

- Documents can be accessed via UHN intranet> Blood and Marrow Transplant Program> UHN BMT Program documents> Immune Effector Cell Therapy> Doc by File type
  - See SOP 17.2\_01 Cytokine Release Syndrome (CRS)
  - See SOP 17.3\_01 CAR-T Cell Related Encephalopathy Syndrome (CRES)
  - See Protocol 17.2.1 Cytokine Release Syndrome (CRS) Grading and Management
  - See Protocol 17.3.1 Management of CAR-T Cell Related Encephalopathy Syndrome (CRES)
  - See Protocol 17.3.5 Management of Seizures (Immune Effector Cell Therapy)
  - See Protocol 17.1.9 Management of Hematophagocytic Lymphocytosis (HLH) or Macrophage Activation Syndrome (MAS) Associated with Immune Effector Cell (IEC) Therapy
  - See Protocol 17.1.10 Management of Cardiovascular Toxicity IEC
- CAR-T cell-related encephalopathy syndrome (CRES)/immune effector cell-associated neurotoxicity syndrome (ICANS) - Symptoms include headache, aphasia, confusion, delirium, altered wakefulness, dysphasia, ataxia, apraxia, tremor, hallucination, incontinence, paralysis of limbs and/or seizures. Median onset is 9 days post infusion. However, there are two peaks. The 1<sup>st</sup> phase (day 0-5): may occur with other CRS symptoms. The 2<sup>nd</sup> phase: (day>5): generally occurs after CRS symptoms have subsided. It is also important to note that neurotoxicity (seizures) may occur as late as the 3<sup>rd</sup> or 4<sup>th</sup> week after infusion. Risk factors for neurotoxicity include high disease burden (>50% blasts) and post treatment CRS  $\geq$  grade 3.

#### Management of CRES/ICANS:

- Documents can be accessed via UHN intranet> Blood and Marrow Transplant Program> UHN BMT Program documents> Immune Effector Cell Therapy> Doc by File type
- See SOP 17.2\_01 Cytokine Release Syndrome (CRS)
- See SOP 17.3\_01 CAR-T Cell Related Encephalopathy Syndrome (CRES)
- See Protocol 17.2.1 Cytokine Release Syndrome (CRS) Grading and Management
- See Protocol 17.3.1 Management of CAR-T Cell Related Encephalopathy Syndrome (CRES)
- See Protocol 17.3.5 Management of Seizures (Immune Effector Cell Therapy)
- See Protocol 17.1.9 Management of Hematophagocytic Lymphocytosis (HLH) or Macrophage Activation Syndrome (MAS) Associated with Immune Effector Cell (IEC) Therapy
- See Protocol 17.1.10 Management of Cardiovascular Toxicity IEC

### ***6.3 Radiation Therapy***

Radiation therapy is a routine part of ALL treatment. Radiotherapy plays a role in the control of known CNS leukemia, and in pre-transplant conditioning. Radiotherapy plays less of a role in prophylaxis of CNS leukemia if adequate prophylactic IT chemotherapy has been administered.

### ***6.4 Other Therapy***

#### ***6.4.1 Ongoing MRD Monitoring***

Ph+ve molecular testing also plays an important role in ongoing, post-remission, minimal residual disease (MRD) assessment (see section 8. below). Prospective monitoring of MRD has the potential to identify patients at risk of relapse. The best frequency for molecular assessment and the best source of cells for testing (blood or marrow) is unclear; however, at the current time, molecular analyses are performed routinely every 3 months.

#### ***6.4.2 Autologous and allogeneic stem cell transplantation (SCT)***

There is currently no indication for autologous SCT in ALL.

AlloSCT-

- Allogeneic transplantation is a treatment option for patients with ALL in CR1 with high-risk features including high-risk cytogenetic (Ph+/MLL) or molecular phenotypes (including Ph-like), or high-risk clinical features at presentation (such as high WBC).
- Beyond first complete remission, alloSCT is the optimal option for eligible patients with ALL who achieve a second remission

### ***6.5 Oncology Nursing***

Refer to [general oncology nursing practice](#)

## **7. Supportive Care**

### ***7.1 Patient Education***

ALL patients and their families receive extensive education (by physicians and specialty nurses) at the time of diagnosis. This education is then reviewed and reinforced during their inpatient and outpatient treatment. Additional teaching occurs prior to and at the time of initial discharge, and this teaching is reviewed during outpatient follow up.

An extensive patient education package which covers all aspects of their care has been prepared for this patient group.

### ***7.2 Psychosocial Care***

Refer to [general psychosocial oncology care guidelines](#)

### ***7.3 Symptom Management***

Refer to [general symptom management care guidelines](#)

### ***7.4 Clinical Nutrition***

Refer to [general clinical nutrition care guidelines](#)

### ***7.5 Palliative Care***

Refer to [general oncology palliative care guidelines](#)

## **8. Follow-up Care**

ALL patients that proceed to allogeneic SCT are followed by the alloSCT service.

ALL patients that do not proceed to alloSCT are supervised closely by the leukemia service during the completion of their induction, CNS phase, intensification, and maintenance/continuation chemotherapy, and are thereafter followed on an ongoing basis. Patients are seen every three months for two years, then every 6 months for 1-2 years, and yearly thereafter with careful review of bloodwork and clinical status. For patients with a specific molecular abnormality that can be detected by PCR (e.g. Ph+ve) or by FISH (e.g. MLL), the best frequency for molecular assessment and the best source of cells for testing (blood or marrow) is unclear. However, at the current time, molecular analyses are usually performed every 3 months.

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