PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

LEUKEMIA

ACUTE LYMPHOBLASTIC LEUKEMIA
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1. Introduction
These guidelines relate to the management of ALL as currently practiced at Princess Margaret Hospital. 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 FAB classification was based on morphology and immunophenotyping:

- ALL-L1: small uniform cells
- ALL-L2: large varied cells
- ALL-L3: large varied cells with vacuoles (Burkitt-like)

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 WHO classification which is based on immunophenotyping plus cytogenetics.

The WHO classification:
1. Acute lymphoblastic leukemia/lymphoma (Former FAB L1/L2)
   i. Precursor B acute lymphoblastic leukemia/lymphoma.
   Cytogenetic subtypes:[19]
   - t(12;21)(p12;q22) TEL/AML-1
   - t(1;19)(q23;p13) PBX/E2A
   - t(9;22)(q34;q11) ABL/BCR
• t(V,11)(V;q23) V/MLL

ii. Precursor T acute lymphoblastic leukemia/lymphoma

2. Burkitt's leukemia/lymphoma Synonyms:Former FAB L3

3. Biphenotypic acute leukemia

5ii. Cytogenetics
The cytogenetics of adult ALL is considerably less complex than is that of pediatric ALL, or of adult AML.

The key treatment-changing considerations in adult AML 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).

5iii. Molecular
Molecular testing at the time of diagnosis in ALL, is generally restricted to determining Ph chromosome positivity.

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 6. and 8. below).

6. Management

6.1 Management Algorithms

Based on an assessment of prognostic factors, an individualized treatment plan is chosen.

^B-ALL/T-ALL - Prognostic factors

Age > 35 years
> 4 weeks to CR
LKC > 30 bil/L (B ALL)
LKC > 100 bil/L (T ALL)
Cytogenetics Ph+ t(9;22) (30 % adults)
translocations involving MLL, myc
hypodiploidy (mostly pediatric)

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

SCT indications are found in 6.4 below.
Chemotherapeutic approaches to relapsed/refractory disease are found in 6.2.1 below.

6.2 Chemotherapy
Newly diagnosed patients are considered in section 6.2.1. Non-responding and relapsed/refractory disease is 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 (ie. mediastinal mass with actual or impending SVC or airway obstruction. Prophylactic CNS therapy is included routinely.

The PMH 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 Hyper-CVAD 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 Hyper-CVAD parts 1A and 1B.

6.2.1.1-4 The PMH DFCI-based protocols:
The DFCI protocols are defined by Ph status and by age:

6.2.1.1

DFCI protocol – Less than 60 years of age, Philadelphia Negative

Protocol: Less than 60 years of age, Philadelphia Negative

Induction: Inpatient Induction Chemotherapy Preprinted Orders

<table>
<thead>
<tr>
<th>Induction Phase (29 days)</th>
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<tbody>
<tr>
<td>Vincristine 2 mg IV or Vinblastine 10 mg IV (neuropathy) Days 1, 8, 15, &amp; 22</td>
</tr>
<tr>
<td>Doxorubicin 30 mg/m²/day IV (For LVEF 50% or greater) Days 1, 2 (Note: For LVEF 40-49%, give Dexrazoxane [Zinecard®] 300 mg/m²/day pre-Doxorubicin on Days 1, 2)</td>
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<td>Methotrexate (MTX) 4 g/m² IV Day 3</td>
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</tr>
<tr>
<td>L-asparaginase 25,000 U/m² IM D5</td>
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<tr>
<td>Prednisone 10 mg/m² po qid or methylprednisolone 8 mg/m² IV qid Days 1-29</td>
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<td>Ara-C 70 mg IT Day 1 (or when no peripheral blasts)</td>
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<td>MTX 12 mg/Ara-C 40 mg/ hydrocortisone 15 mg IT Day 15, 29</td>
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</table>
### CNS Phase (21 days)
Vincristine 2 mg IV or Vinblastine 10 mg IV (neuropathy) D0
Doxorubicin 30 mg/m²/day IV (LVEF 50% or greater) D0
6-mercaptopurine 50 mg/m2/day po x 14 days (D0-13)
MTX 12 mg/Ara-C 40 mg/ hydrocortisone 15 mg IT D0, 3, 7, & 10

### Intensification Phase (30 weeks; ten 3-week cycles)
Vincristine 2 mg IV or vinblastine 10 mg IV (neuropathy) week 1 (D1)
Doxorubicin 30 mg/m² IV (LVEF 50% or greater) week 1 (D1) for cycles 1-7 then
MTX 30 mg/m² IV or IM 24h post-MTX for cycles 8-10
6-mercaptopurine 50 mg/ m²/day po x 14 days starting week 1 (D1-14)
Dexamethasone 9 mg/m² po bid x 5 days starting week 1 (D1-5)
L-asparaginase 12,500 U/m² 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/m²/day po x 14 days starting week 1 (D1-14)
Dexamethasone 6 mg/m² po bid x 5 days starting week 1 (D1-5)
Methotrexate 30 mg/m² 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)
NaHCO₃ 1000 mg po tid x 3 days (induction; D1-3)
Fluconazole 400 mg po daily (induction; start D4)
Septra SS 2 tabs po three times weekly (qMonday, Wednesday, & Friday)
Acyclovir 400 mg po BID (induction; start D1)
Bisphosphonates, calcium, and vitamin D
Enoxaparin 40/60mg sc daily (intensification)
Bone mineral density & MRI hips and knees (end of intensification)
Baseline MUGA scan
6.2.1.2

DFCI protocol – **Less than 60 years of age, Philadelphia Positive**

Protocol: **Less than 60 years of age, Philadelphia Positive**

Induction: **Inpatient Induction Chemotherapy Preprinted Orders**

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## 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/m²/d po x 14 days starting week 1 (D1-14)
- **Dexamethasone**: 6 mg/m² po bid x 5 days starting week 1 (D1-5)
- **Methotrexate**: 30 mg/m² 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)
- **NaHCO3**: 1000 mg po tid x 3 days (induction; D1-3)
- **Micafungin**: 50 mg IV daily (induction; start D4)
- **Septra SS**: 2 tabs po three times weekly (qMonday, Wednesday, & Friday)
- **Acyclovir**: 400 mg po BID (induction; start D1)
- **Bisphosphonates, calcium, and vitamin D**
- **Enoxaparin 40/60mg sc daily** (intensification)
- **Bone mineral density & MRI hips and knees** (end of intensification)
- **Baseline MUGA scan**
### Induction Phase (28 days)
- Vincristine 2 mg IV or vinblastine 10 mg IV (neuropathy) D1, 8, 15
- Doxorubicin 30 mg/m²/day IV (LVEF 50% or greater) Days 1,2 (Note: For LVEF 40-49%, give Dexrazoxane \{Zinecard®\} 300 mg/m²/day pre-Doxorubicin on Days 1, 2)
- Methotrexate (MTX) 40 mg/m² IV Day 3
- Leucovorin 15 mg IV q6h x 4 doses starting 24 h post MTX
- L-asparaginase 12,000 U/m² IM D4
- Dexamethasone 40 mg po/IV daily Days 1-4, Days 9-12
- Ara-C 70 mg IT Day 1 (or when no peripheral blasts)
- MTX 12 mg/Ara-C 40 mg/ hydrocortisone 15 mg IT Day 15

### CNS Phase (21 days)
- Vincristine 2 mg IV or vinblastine 10 mg IV (neuropathy) D1
- Doxorubicin 30 mg/m²/d IV (LVEF 50% or greater) D1
- 6-mercaptopurine 50 mg/m²/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/m² IV (LVEF 50% or greater) week 1 (D1) for cycles 1-7
- 6-mercaptopurine 50 mg/m²/d po x 14 days starting week 1 (D1-14)
- Dexamethasone 9 mg/m² po bid x 5 days starting week 1 (D1-5)
- L-asparaginase 6000 U/m² 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/m²/d po x 14 days starting week 1 (D1-14)
- Dexamethasone 6 mg/m² po bid x 5 days starting week 1 (D1-5)
- Methotrexate 30 mg/m² po on weeks 1, 2, & 3
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### 6.2.1.4

**DFCI protocol – *Age 60 years and greater, Philadelphia positive***

**Protocol:** *Age 60 years and greater, Philadelphia positive*

**Induction:** *Inpatient Induction Chemotherapy Preprinted Orders*

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6.2.1.5
Relapsed/refractory disease

DFCI failures generally proceed to Hyper-CVAD:

PMH-modified version of HYPER-CVAD PROTOCOL OUTLINE (PMH, July 2010)

Patient Eligibility:
1) ALL, relapsed after, or refractory to, DFCI induction therapy
2) ALL in which DFCI regimen is contraindicated
3) T-ALL with large mediastinal mass*
4) Age up to 70 years

* 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 Hyper-CVAD 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 Hyper-CVAD parts 1A and 1B.

Protocol, ALL Treatment with HYPER-CVAD (A and B)

Hyper-CVAD Part A

Inpatient Induction Chemotherapy Preprinted Orders HYPER-CVAD A

Cyclophosphamide 300 mg/m² IV over 3h Q12H x 6 doses Days 1-3 (3 days total = 1800 mg/m²)
Doxorubicin 50 mg/m² IV on Day 4, 12 h after last dose of Cyclophosphamide (LVEF 50% or greater).
(Note: For LVEF 40-49%, give Dexrazoxane {Zinecard®} 500 mg/m²/day pre-Doxorubicin)
Vincristine 2 mg IV on Day 4 and Day 11
L-asparaginase 25,000 U/m² (max. 50,000 U) IM on Day 5

[Only for patients NOT receiving a Tyrosine Kinase Inhibitor (e.g. Imatinib {Gleevec®})]
Dexamethasone 40 mg PO/IV daily x 4, Days 1-4 and Days 11-14
CNS prophylaxis^:
Methotrexate 12 mg intrathecal Day 2
Ara-C 70mg intrathecal Day 11

Hyper-CVAD Part B

Inpatient Induction Chemotherapy Preprinted Orders HYPER-CVAD B

Methotrexate 1 g/m² IV over 24h, on Day 1 (given with leucovorin rescue)
(Or may give Methotrexate 40 mg/m² IV if edema or effusions)
Cytarabine (Ara-C) 3 g/m² IV over 3 hours Q12H x 4 doses on Day 2 and 3
(For patients 60 years of age and over: Cytarabine 1.5 g/m² IV over 3 hours Q12H x 4 doses on Day 2 and 3

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 10⁹/L
3. the platelet count is > 100,000 x 10⁹/L

NB. 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

6.3 Radiation Therapy

Radiation therapy is used for the control of known CNS leukemia, and in pre-transplant conditioning. Current studies demonstrate that the routine use of radiation in patients without CNS disease may not be needed and can be replaced with intrathecal chemotherapy.

6.4 Other Therapy

Autologous and allogeneic stem cell transplantation (SCT).

Auto SCT-
There is currently no indication for autoSCT 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, or high-risk clinical features at presentation (such as high Lkc)

- 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
APL 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 alloSCT 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. Specifically, patients with specific molecular abnormality that can be detected by PCR (eg. Ph+ve) or by FISH (eg. MLL), are seen every three months for two years, then every 6 months for 1-2 years, and yearly thereafter. In addition to careful review of bloodwork and clinical status, molecular analyses are performed routinely for the first 3-4 years.

Patients lacking such abnormalities are followed on a similar schedule, with careful review of bloodwork and clinical status.