

Acute Lymphoblastic Leukemia (Adult) Including Lymphoblastic lymphoma

Updated April 2008 by Dr. Richard Wells*

Updates: Minor changes only

Introduction

Acute lymphocytic leukemia (ALL) is a relatively rare cancer in adults with an estimated annual incidence of 1.3/100,000 [1]. The peak incidence of ALL is age 10 with a smaller peak > age 70 years. The incidence in African-Americans appears to be approximately half that in Caucasians.

Diagnosis

ALL is now diagnosed and classified according to the WHO classification of neoplastic disease of hematopoietic and lymphoid tissues [2]. ALL is defined by the presence of $\geq 20\%$ lymphoblasts in the marrow or peripheral blood. This is a change from the previous FAB classification, which required $\geq 30\%$ blasts [3]. The relationship between ALL and lymphoblastic lymphoma remains unclear. Under the WHO classification both are grouped together under the category lymphoblastic leukemia/lymphoma [2]. Patients who present as lymphoma typically have a precursor T-cell immunophenotype (80%), whereas patients who present as leukemia generally have a precursor B-cell immunophenotype.

The FAB classified ALL into 3 morphologic types (L1, L2, L3) [3]. The distinction of L1 from L2 is subjective and has not been shown to be of clinical importance. For this reason, this distinction has been removed in the WHO system [2]. The L3 type (Burkitt's leukemia/lymphoma) remains classified as a distinct entity as it has characteristic morphology, immunophenotype and genotype. L3 lymphoblasts are characteristically homogeneous, of medium size with dispersed chromatin, multiple nucleoli, and a moderate amount of deep blue cytoplasm with sharply defined vacuoles. L3 blasts do not typically express TdT. Their typical flow pattern is: CD19⁺, CD20⁺, CD22⁺, CD79a⁺, SIg⁺.

It is important to distinguish L3 from other ALL, as they must be treated differently (**see Burkitt's lymphoma**). The differential diagnosis of ALL includes:

- ❖ Reactive lymphocytosis
 - ❖ Acute myeloid leukemia
 - ❖ Mantle cell lymphoma, blastic variant
 - ❖ Gamma-Delta T-cell hepatosplenic lymphoma
 - ❖ Non-hematologic malignancies (Rhabdomyosarcoma, Ewing's small cell lung cancer)
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Baseline Investigations

As for acute myelogenous leukemia, with the addition of molecular assessment of blood and/or bone marrow by RT-PCR for the BCR-ABL gene fusion.



Prognosis & Staging

With currently available therapeutic regimens, complete response rates range from 65% to 70% [4]. Long-term survival rates, however, remain unsatisfactory at 20%-45%. Poor prognostic factors in most published series include [5]:

- ❖ Age (continuous variable, but age > 30 often cited)
- ❖ Immunophenotype (c-ALL and T lineage superior to null or mature B)
- ❖ WBC > 30 x 10⁹/L
- ❖ Time to CR > 4 wks
- ❖ Karyotype

Karyotype is particularly important prognostically [6]. Data from 6 studies including 1352 patients are summarized below.

Risk	Cytogenic Abnormality	5-Year CCR Rate
Unfavorable	t(9;22), +8, t(4;11) -7, hypodiploid, t(1, 9)	8-25%
Intermediate	Normal, +21, del(9p) or t(9p), hyperdiploid	29-44%
Favorable	Del(6q), del(12p) or t(12p), t(14q11-q13)	76-78%

CCR – Continuous Complete Remission

Treatment

The remainder of this document refers to the management adult ALL other than L3. Please refer to the Burkitt's lymphoma treatment policy for management of ALL-L3.

Many different regimens are used to treat adult ALL [4]. Many derive from protocols studied in children, and few have been compared in randomized trials. Results of single arm trials from different institutions are difficult to compare as the proportion of high-risk patients may differ. The following table summarizes results from a number of published trials.

Group Regimen Ref.	MDACC Hyper-CVAD [7]	GMALL 03/84 [8]	MRC ALL1X [9]	LALA LALA87 [10]	CALGB 9111 [11]	MSKCC L2-L17M [12]	PMH/UHN Protocol C [13]
N	204	569	266	572	199	199	70
%Ph1+	16%	NS	NS	NS	22%	9%	NS
%CR	91%	75%	87%	76%	85%	82%	76%
%3yr OS	50%	43%	31%	33%	50%	43%	38%
%5yr OS	39%	39%	26%	27%	42%	37%	32%

MDACC	MD Anderson Cancer Center
GMALL	German Multicenter Study Group for Adult ALL
MRC	Medical Research Council (UK)
LALA	Leucémie Aiguë Lymphoblastique de l' Adulte
CALGB	Cancer and Leukemia Study Group B
MSKCC	Memorial Sloan Kettering Cancer Center
PMH/UHN	Princess Margaret Hospital/University Health Network

These regimens are based on common principles of ALL treatment, namely:

1. Intensive multi-agent remission induction chemotherapy, including some combination of an anthracycline, vincristine, corticosteroid, cyclophosphamide, asparaginase, methotrexate, and cytarabine
2. Further intensive postremission therapy comprising allogeneic BMT or chemotherapy
3. CNS prophylaxis with intrathecal chemotherapy and/or cranial irradiation.



Ph+ ALL

The overall rate of Ph/BCR-ABL positive ALL in adult ALL series is 20-30%. Patients with Ph+ ALL treated with conventional chemotherapy have a poor prognosis, with survival 0-6% at 3 years after diagnosis. By contrast, leukemia-free survival rates of ~50% and ~40% are reported for Ph+ ALL following related donor and unrelated donor allogeneic bone marrow transplantation, respectively. Patients with Ph+ ALL should therefore be evaluated for related- or unrelated donor allogeneic transplantation.

Imatinib shows promise in the treatment of Ph+ ALL. Ph+ ALL cells are exquisitely sensitive to imatinib in vitro, and the combination of imatinib with daunorubicin, cytarabine, or corticosteroids demonstrates synergistic effects [14]. Early clinical trial reports indicate that inclusion of imatinib in the induction and intensification phases of ALL therapy improve CR rates [15] and outcome of allogeneic transplantation [16], and may also be effective in management of minimal residual disease following transplant [17]. Our practice is to include imatinib in the induction and/or intensification phases of treatment for Ph+ patients.

Supportive Care

G-CSF administration during induction and consolidation has been shown to decrease the incidence of neutropenic events. In a randomized CALGB trial, G-CSF decreased the number of days in hospital (*22 days vs. 28 days; p = 0.02*) and decreased death rate during remission (*5% vs. 11%; p = 0.04*), but does not influence overall toxicity or survival [11].

Patients who are to be discharged home during the period of neutropenia should be started on G-CSF 300 µg sc daily starting day 5 after each cycle until ANC $1.0 \times 10^9/L$. G-CSF will not be routinely given in hospitalized patients.

Throughout the intensification phase of treatment patients are evaluated weekly with clinical examination and blood work. This treatment entails severe, prolonged immunosuppression, and patients require PCP prophylaxis with Septra or pentamidine. Patients with ALL are not candidates for outpatient oral antibiotic therapy for neutropenic fever.

The Dana Farber protocol includes weekly high-dose asparaginase during the 27-week intensification phase. This drug is known to be thrombogenic and thrombosis rates as high as 20% in patients have been observed in patients on this protocol [18]. While it is not clear if prophylactic antithrombotic therapy has a role in ALL treatment, patients should be monitored clinically and treated for thrombosis with full therapeutic anticoagulation if indicated.

Stem Cell Transplantation

While it is accepted that autologous stem cell transplantation does not improve outcome in ALL, the role of allogeneic stem cell transplantation in the treatment of this disease remains controversial. There have been no trials in the field of allogeneic BMT in which patients with a matched sibling donor have been randomized between allogeneic BMT vs chemotherapy. In the absence of a true randomization, genetic randomization is an established way of comparing allogeneic BMT with chemotherapy or ABMT. In this approach, the outcomes of patients for whom an HLA matched sibling donor is available are compared with outcomes of patients lacking a sibling donor, on an intent-to-treat basis. A single analysis of this type has been published for ALL [19]; this study showed no significant improvement in 5 year survival for the transplant group overall, but subgroup analysis indicated an advantage for transplant in patients with high-risk ALL. A more recent retrospective donor vs no donor comparison suggested that only patients with Ph+ ALL benefit from allogeneic BMT [20]. For patients who are candidates for allogeneic BMT, referral to a BMT centre should be made immediately after successful induction of complete remission. It is important to confer with transplant physicians prior to initiation of the CNS prophylaxis phase of treatment, so that adjustment of irradiation schedule can be made if necessary. Irradiation may be omitted from the CNS prophylaxis phase if a patient is to receive total body irradiation as part of the BMT conditioning regimen.



Odette Cancer Centre Policy

- ❖ Patients with ALL should be enrolled in clinical trials where available (especially those with Ph+ ALL).
- ❖ Patients not eligible for clinical trials will be managed with the Dana-Farber protocol (**Appendix B**).
- ❖ Patients under age 55 with one or more high risk feature should have HLA testing performed early in the course of their treatment and should be referred to discuss alloBMT if a donor is identified. High-risk features include age > 30, WBC > 30, time to CR > 4 weeks, or unfavorable karyotype including presence of the Philadelphia chromosome (**see Prognosis and Staging, pg. 2**).

Monitoring and Assessment of Response

Patients will have bone marrow aspiration repeated 4 weeks after starting therapy. Cytogenetics and or molecular studies should be performed if the patient is known to have an abnormal karyotype. Patients with ≤ 5% blasts in the marrow will be considered to be in complete remission (CR). Patients who achieve a CR after 4 weeks will continue on with therapy. Patients with 6-20% blasts may continue on with treatment, but are at high risk of progression and should be considered for allogeneic transplantation early after achieving remission. Patients with > 20% blasts should have treatment discontinued and be considered for experimental therapy.

Treatment of Refractory or Relapsed Disease

The prognosis of patients who fail to achieve remission or who relapse is poor [21]. A response can be obtained in 40-60% of cases, but responses are short, typically 2-7.5 months. Outcome is particularly poor for patients with a first CR responses lasting ≤ 18 months. In such cases the chance of long-term survival is < 5%.

Patients who fail primary therapy should be offered enrollment in clinical trials. If no studies are available, patients should be re-induced with multi-agent chemotherapy with a plan to proceed to allogeneic transplant if a donor (related or unrelated) is available. In such cases, long-term survival rates of 12%-43% can be observed. For patients failing after the Dana Farber regimen, Protocol C will typically be used.

References

1. *Canadian Cancer Statistics*. 2001.
2. Harris, N.L., et al., *World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997*. *J Clin Oncol*, 1999. **17**(12): p. 3835-49.
3. Bennett, J.M., et al., *Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group*. *Ann Intern Med*, 1985. **103**(4): p. 620-5.
4. Kantarjian, H.M., *Adult acute lymphocytic leukemia. Introduction and questions related to current programs*. *Hematol Oncol Clin North Am*, 2000. **14**(6): p. 1205-8, VII.
5. Hoelzer, D., et al., *Intensified therapy in acute lymphoblastic and acute undifferentiated leukemia in adults*. *Blood*, 1984. **64**(1): p. 38-47.
6. Wetzler, M., *Cytogenetics in adult acute lymphocytic leukemia*. *Hematol Oncol Clin North Am*, 2000. **14**(6): p. 1237-49.
7. Kantarjian, H.M., et al., *Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia*. *J Clin Oncol*, 2000. **18**(3): p. 547-61.
8. Hoelzer, D., et al., *Follow-up of the first two successive German multicentre trials for adult ALL (01/81 and 02/84)*. *German Adult ALL Study Group*. *Leukemia*, 1993. **7 Suppl 2**: p. S130-4.
9. Durrant, I.J., et al., *Results of Medical Research Council trial UKALL IX in acute lymphoblastic leukaemia in adults: report from the Medical Research Council Working Party on Adult Leukaemia*. *Br J Haematol*, 1993. **85**(1): p. 84-92.



10. Fiere, D., et al., *Adult acute lymphoblastic leukemia: a multicentric randomized trial testing bone marrow transplantation as postremission therapy. The French Group on Therapy for Adult Acute Lymphoblastic Leukemia.* J Clin Oncol, 1993. **11**(10): p. 1990-2001.
11. Larson, R.A., et al., *A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111.* Blood, 1998. **92**(5): p. 1556-64.
12. Gaynor, J., et al., *A cause-specific hazard rate analysis of prognostic factors among 199 adults with acute lymphoblastic leukemia: the Memorial Hospital experience since 1969.* J Clin Oncol, 1988. **6**(6): p. 1014-30.
13. Stewart, K., et al., *Adult acute lymphoblastic leukemia: the value of therapy intensification.* Leuk Lymphoma, 1991. **4**: p. 103-110.
14. Hallbook, H., et al., *In vitro activity of imatinib in cells from patients with adult acute lymphoblastic leukemia.* Anticancer Drugs, 2005. **16**(6): p. 631-4.
15. Towatari, M., et al., *Combination of intensive chemotherapy and imatinib can rapidly induce high-quality complete remission for a majority of patients with newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia.* Blood, 2004. **104**(12): p. 3507-12.
16. Lee, S., et al., *The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia.* Blood, 2005. **105**(9): p. 3449-57.
17. Wassmann, B., et al., *Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL).* Blood, 2005. **106**(2): p. 458-63.
18. Cserti, C., et al., *Thrombotic events in adults with acute lymphoblastic leukemia (Abstract#2734).* Blood, 2005. **104**(11): p. 747a.
19. Sebban, C., et al., *Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia.* J Clin Oncol, 1994. **12**(12): p. 2580-7.
20. Gupta, V., et al., *The role of allogeneic bone marrow transplantation in adult patients below the age of 55 years with acute lymphoblastic leukemia in first complete remission: a donor vs no donor comparison.* Bone Marrow Transplant, 2004. **33**(4): p. 397-404.
21. Garcia-Manero, G., et al., *Salvage therapy for refractory or relapsed acute lymphocytic leukemia.* Hematol Oncol Clin North Am, 2001. **15**(1): p. 163-205.