1

Prognostic Markers and Models in Acute Lymphoblastic Leukemia

Dieter Hoelzer

University of Frankfurt, Germany

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease characterized by subgroups with different biological and clinical features and cure rates. They have prognostic impact for the achievement of remission or the remission duration. There are two phases to evaluate prognostic factors: (1) Patient's characteristics at diagnosis, and (2) patient's response to treatment (Table 1.1). Pretherapeutic prognostic features are age, initial white blood cell (WBC) count, immunophenotype, and abnormal cytogenetics or molecular genetics. Response parameters are achievement of complete remission, particularly molecular remission, and time to achieve a complete remission and molecular remission. The aim of evaluating prognostic factors in ALL is to stratify patients into good and poor risk groups and to adapt different treatment strategies accordingly. One important decision in adult ALL is, thereby, whether a patient should have an allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission or not.

1) What is the prognostic value of patient's age at diagnosis in adult ALL, and what are the therapeutic implications?

Expert Perspective: Advancing age is undoubtedly associated with poorer outcome in all studies. In adolescents and young adults (AYAs, i.e. adults up to age 40), pediatric-inspired intensive protocols are applied. Thereafter, the protocol intensity is decreased. Currently, treatment protocols for elderly (> 60 years) are with less intensive chemotherapy backbone combined with immunotherapies and/or with tyrosine kinase inhibitors (TKIs) in Ph+ ALL (discussed in chapters on treatment in B- and T-ALL). Patients older than age 60 years have a substantially poorer outcome due to comorbidities and an increasing incidence of adverse risk factors. All patients are subject to CNS screening by flow cytometry and prophylaxis.

Cancer Consult: Expertise in Clinical Practice, Volume 2: Neoplastic Hematology & Cellular Therapy,
Second Edition. Edited by Syed A. Abutalib, Maurie Markman, James O. Armitage, and Kenneth C. Anderson.

Table 1.1 Prognostic factors for risk stratification of adult acute lymphoblastic leukemia (ALL)[1].

Prognostic factors	B-lineage			T-lineage	
Pretherapeutic parameters	**Good**	**Intermediate**	**Adverse**	**Good**	**Adverse**
• Age	**< 35 years**	**35–50 years**	**> 55–60 years** **> 70 years elderly/frail**		
• White blood cell count	**< 30,000/μL**		**> 30,000/μL**		
• Organ involvement[3]					
• Immunophenotype				Thymic (CD1a+, TAL/LMO)	Early T (CD1a−, sCD3−) Mature T (CD1a−, sCD3+)
• Molecular/subgroups cytogenetics	**Ph+/BCR–ABL1 t(9;22) (q34;q11.2)** IgH-MYC+, t(8,14)(q24;q32) TEL–AML1 (?) HOX11[2] NOTCH1[2] (?)	***IKZF1*-Deletion** 7p focal deletions/ mutations MLL rearranged	**Ph-like** **ALL1–AF4 / t(4;11)** t(1;19)/E2A–PBX (?) Complex aberrations (?)		HOXA aberrations CALM-AF10 Complex aberrations (?)
Treatment response					
Prednisone response	Good		Poor		
Time to complete remission	**Early (<2–3 weeks)**		**Late (> 3–4 weeks)**		
MRD[4] after induction	**Negative < 10^{-4}**		**Positive > 10^{-4}**		

[1]Generally accepted factors are printed in **bold**.
[2]Overexpression of genes.
[3]Organ involvement, particularly central nervous system involvement, and mediastinal tumors have lost their adverse impact with recent treatment strategies.
[4]MRD, measurable residual disease.

2) Does WBC at diagnosis still have a prognostic impact in B-ALL and T-ALL?

Expert Perspective: Elevated WBC at diagnosis (> 30,000–50,000/mL) is a poor prognostic feature, especially deleterious in precursor B-cell ALL. Subtype Ph-like ALL (provisional category 2016 WHO classification) has higher WBC count at presentation, higher measurable residual disease at the end of induction therapy and inferior overall survival (Chapter 2). In T-ALL a high WBC > 100,000 was considered a poor prognostic factor but with an ongoing more-intensive protocol these adverse factors seem to be abrogated (Chapter 3).

3) What is the relevance of cytogenetic and molecular markers for treatment decisions?

Expert Perspective: Ph+ ALL with the t(9;22) translocation and the BCR–ABL fusion transcript is the most prevalent cytogenetic abnormality in adults with B-ALL, increasing from < 3% in children up to 40–50% in adults over the age of 50–60 years. Ph+ ALL was so far the poorest ALL subtype, with a survival rate at 5 years of < 10% with chemotherapy and < 30% with allo-HCT. Targeted therapy with tyrosine kinase inhibitors (TKIs) in combination with chemotherapy has changed the prognosis landscape dramatically; now the complete remission rates approach levels > 90% and survival > 50–70% in most series. Allo-HCT is still a curative approach with a survival rate of 50–70% for ALL.

4) Which of the following statements about Ph-like ALL is correct?

a) It is more common in adults than in children.
b) It is associated with superior outcomes without allogeneic transplant.
c) There is no role of *JAK-2* inhibitor therapy in B-ALL.
d) All of the above.

Expert Perspective: Ph-like ALL is characterized by a gene-expression profile like that of *BCR::ABL1*-positive ALL but lacks the *BCR::ABL1* fusion protein, or t(9;22), by cytogenetic, FISH, or molecular analysis and alterations of lymphoid transcription factor genes. It is associated with poor prognosis and is seen in 10–20% of pediatric cases and 20–30% of adult cases of B-ALL. It is included as a provisional entity in the 2016 WHO Classification. A variety of different genetic abnormalities are identified in this entity, but they all converge on pathways that are potentially responsive targeted therapy added to conventional chemotherapy, one of them being *JAK-2* inhibitor therapy (more on this topic in Chapter 2).

Tyrosine Kinase Rearrangements

A feature of Ph-like ALL is the presence of fusion genes involving a tyrosine kinase: the *ABL*-class and *JAK2* arrangements. In adolescents and adults, *ABL*-class rearrangements occur in about 10% and *JAK2* rearrangements are detected in 7–8%. Patients with *ABL*-class rearrangements should receive additional TKI therapy. Patients with *JAK2* rearrangements may be candidates for additional *JAK2*-inhibitor therapy.

Diagnosis of Ph-like ALL

Diagnosis of a Ph-like ALL is difficult. There are low density classifiers (LDA) to identify predictor genes assays of either 8 or 9 gene signatures. Since the diagnosis of Ph-like ALL is not trivial and is not available at first diagnosis, commonly specific drugs are added later. There are, however, studies to identify Ph-like ALL genetics stratification at diagnosis as in the COG trial (Chapter 2).

Ph-like ALL has poor prognosis, and patients often present with adverse features such as high WBC. These patients should be considered for frontline allo-HCT. Whether the addition of immunotherapy as in Ph+ ALL improves the poor outcome of Ph-like ALL remains an open question (Chapter 5).

Correct Answer: A

5) In current clinical practice, what are the targetable surface antigens in B-ALL?

Expert Perspective: A variety of targeted monoclonal antibody therapies directed against surface antigens, particularly CD20 (rituximab and other anti-CD 20 antibodies), CD19 (blinatumomab and chimeric antigen receptors T cells), and CD22 (inotuzumab ozogamicin). These targeted antibodies have been and are further being explored (Chapter 2).

6) What is the prognostic value of CD20, CD22, and CD19 surface expression in B-ALL?

Expert Perspective: The question arises of whether antigen expression itself within an immunologically defined subtype is a prognostic marker.

- **Surface CD20 expression**, observed in about 40% of adult pre-B-ALL and common B-ALL, had an adverse prognostic impact, but the therapy with rituximab has apparently overcome the potential adverse influence.
- **Surface CD22** is expressed on leukemic blasts in 90–100% of B-ALL and is an excellent target for the inotuzumab ozogamicin. It seems, however, that the antigen expression of CD22 per cell as a prognostic impact has a better outcome for highly expressed CD22 as long as therapy against CD22 is utilized. In the INO-VATE study, the rate of complete remission was higher with inotuzumab ozogamicin than with standard therapy, and a higher percentage of patients in the inotuzumab ozogamicin group had results below the threshold for MRD. Both progression-free and overall survival were longer with inotuzumab ozogamicin. However, veno-occlusive liver disease was a major adverse event associated with inotuzumab ozogamicin. This agent is a humanized CD22-directed monoclonal antibody-drug conjugate, which is composed of the IgG4 kappa antibody inotuzumab (which is specific for human CD22), a calicheamicin component (a cytotoxic agent that causes double-stranded DNA breaks), and an acid-cleavable linker that covalently binds the calicheamicin to inotuzumab. After the antibody-drug conjugate binds to CD22, the CD22-conjugate complex is internalized and releases calicheamicin. Calicheamicin binds to the minor groove of DNA to induce double strand cleavage and subsequent cell cycle arrest and apoptosis.
- **Surface CD19** is also expressed on nearly 100% B cells. Blinatumomab is a bispecific T-cell engager (BiTE) that binds to CD19 expressed on B cells and CD3 expressed on T cells. It

activates endogenous T cells by connecting CD3 in the T-cell receptor complex with CD19 on B cells (malignant and benign), thus forming a cytolytic synapse between a cytotoxic T cell and the cancer target B cell. Blinatumomab mediates the production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in lysis of CD19-positive cells. In the TOWER study, treatment with blinatumomab resulted in significantly longer OS than chemotherapy among adult patients with relapsed or refractory B-cell precursor ALL. CD19 is also target of *ex vivo* gene therapy, namely chimeric antigen receptor T cells. Although the CD19-antigen expression per cell is of prognostic relevance, the greater impact is the loss of CD19 antigen after this therapy, which is associated with failure of targeted therapies and poor outcome (see Chapter 2 for further discussion).

Response Parameters in B-ALL

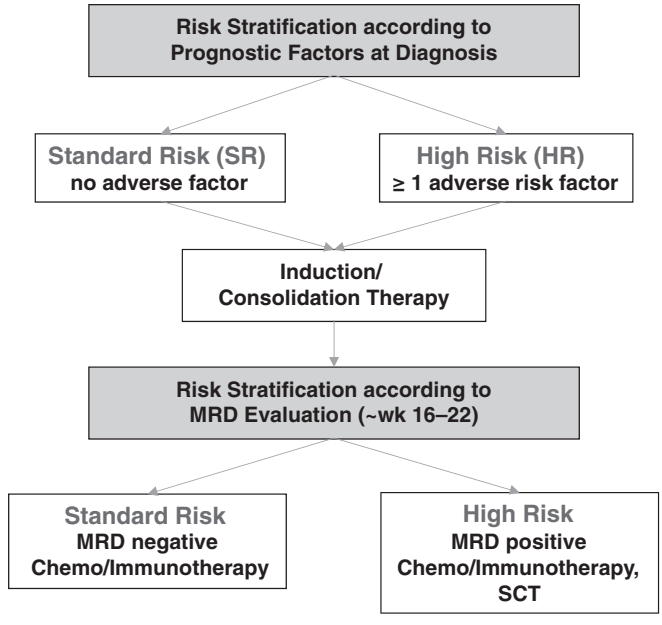
7) Is achievement of first complete remission a prognostic marker for overall outcome, and how important is time to achieve complete remission?

Expert Perspective: Some response parameters after induction therapy are highly predictive for outcomes. For example, time to achieve a complete remission within 3–4 weeks or a molecular complete remission after 14–16 weeks are important. The rate of complete remission is prognostically less relevant since > 95% of children and > 90% of adults achieve a complete remission. Despite favorable complete remission rates in adults, 40–50% eventually relapse. One of the reasons is the limited sensitivity to measure the leukemic cell reduction by cytomorphology. Complete remission is, however, still an important goal and first step toward ensuring success. Therefore, achievement of complete remission is still commonly accepted as endpoint for studies. (See Chapters 2, 4, and 5.)

Risk Stratification in B-ALL

8) What is the purpose of stratification into risk groups?

Expert Perspective: Similar to childhood ALL, several large ALL study groups have defined risk groups in adults. Pretherapeutic prognostic factors and response parameters are used to define risk groups; standard-risk (SR) patients are generally defined as those without any adverse risk factors, whereas high-risk (HR) patients have one or more risk factors (Table 1.1). The aim of these still important prognostic strategies is to identify an SR group with a good outcome (e.g. with an expected > 50% survival probability at five years in adults) and the HR patient group with a less favorable outcome. High-risk patients are generally candidates for an immediate allo-HCT in first complete remission, whereas standard-risk patients in most studies continue with consolidation cycles ± reinduction and maintenance therapy (see Chapter 6). In several study groups, there was also the definition of a very-high-risk (VHR) group in adults, preferentially patients with Ph+ ALL or Ph-like ALL. The prognosis of this Ph+ALL has completely changed with better outcomes using various combinations of chemotherapy, TKIs, immunotherapy ± allo-HCT in first complete remission (Figure 1.1).



- **Minimal residual disease after Ind/Cons is the most important prognostic factor and relevant for treatment decision**
- **Targeted Therapy Applied in B-lineage ALL**
  - **Surface Antigens CD19, CD20, CD22 → Immunotherapy**
  - **Ph+/Ph-like → Tyrosine Kinase Inhibitors (TKI) ± Immunotherapy**

Figure 1.1 Practical approach for treatment stratification in adult B-cell acute lymphoblastic leukemia (ALL).
SCT—allogeneic stem cell transplantation
MRD—measurable residual disease

9) Will the prognostic impact of pretherapeutic risk factors and stratification into risk groups be replaced by measurable residual disease?

Expert Perspective: Clearly not; standard-risk patients have high complete remission rates of 90%, supported by a high rate of MRD clearance, and are spared for allo-HCT. High-risk patients still have lower rates of complete remission by 50–60%, also with a lower MRD rate. They are candidates for allo-HCT in first complete remission, but with the targeted therapy to reduce MRD load further before transplant (see Chapter 2).

The achievement of a complete remission is also relevant since not all patients, for several reasons, have access to MRD evaluation (~15% don't have). Furthermore, many hospitals and treatment centers around the world do not have experienced lab to follow MRD (also for cost reasons), and therefore, the conventional response parameters such as complete remission and CRi (incomplete hematological remission) are still of high prognostic relevance.

Whether the increasing use of immunotherapy will change the prognosis of specific B-ALL subtypes and thereby the indications for allo-HCT also remains currently an open question (see Chapters 2 and 3).

T-lineage ALL

Based on immunophenotyping, T-ALL comprises the subtypes of early T-ALL, thymic (cortical) T-ALL, and mature T-ALL. In the GMALL studies these subtypes were the most relevant prognostic factors.

- **Thymic T-ALL** is CD1a-positive and constitutes about half of the adult T-ALL patients; it has the best prognosis, with complete remission rates ≥95% and overall survival at five years of 60–80% (Table 1.1).
- The other subtypes, early T-ALL and mature T-ALL, have lower rates of complete remission and poorer survivals; both subtypes profit from an allo-HCT in first complete remission (although opinion among experts varies!). However, within the early T-ALL a new subtype has been identified as Early progenitor T-ALL (ETP-ALL), which has the least favorable outcomes (discussed in depth in Chapter 3).

10) Is ETP-ALL clinically and prognostically relevant?

Expert Perspective: ETP-ALL is a newly described provisional entity. The immunophenotype is CDy1a-, CD8-, or CD5 weak or negative. It is characterized by stem cell markers such as CD34, HLA-DR, CD117, and/or myeloid antigens (CD 13, CD33, CD65s). The mutational status of ETP vs non-ETP early T-ALL is characterized by *FLT3 (ITD)* with 25% vs 0% and *NOTCH* mutations with a lower rate of 7% vs 53%, respectively. Importantly, ETP-ALL has poor prognostic marker, although in some studies there is no difference in overall survival between ETP and non-ETP early T-ALL. Some groups observed inferior outcomes for early T-ALL with co-expression of CD13, CD33, and/or CD34; a high expression of the transcription factors *ERG* and/or *BAALC*; and overexpression of *HOX11-L2* and *SIL-TAL1*-positive ALL (Chapter 3).

11) What is the prognostic relevance of molecular markers in relation to the immunophenotypic T-ALL subtypes?

Expert Perspective: The overexpression of *HOX11*, *HOX11L2*, *SIL-TAL1*, and *CALM–AF10* is associated with described subtypes since it represents the maturation states of thymocytes.

- **Low expression of *ERG* and *BAALC*** was associated with favorable outcome as well as overexpression of *HOX11*, which is associated with thymic T-ALL.
- ***NOTCH1*-activating mutations**, which are identified in up to 50% of T-ALL cases, so far have an unclear prognostic relevance. Attempt to be targeted by γ-secretase inhibitors have largely failed due to toxicity. Five percent of T-ALL shows the *NUP214–ABL1* aberration, which may identify a target population for imatinib therapy. Altogether there have been many attempts to stratify T-ALL by genetic markers, mostly based on retrospective analysis, but the impact on prospective risk stratification and different treatment strategies is limited (see Chapter 3).

Recommended Readings

Chiaretti, S., Messina, M., and Foà, R. (2019). BCR/ABL1–like acute lymphoblastic leukemia: how to diagnose and treat? *Cancer* 125: 194–204.

Chiaretti, S., Elias, J., and Dieter, H. (2018). ""Society of Hematologic Oncology (SOHO) State of the Art Updates and Next Questions"-Treatment of ALL". *Clin Lymphoma Myeloma Leuk* 18 (5): 301–310.

Cordo' V., van der Zwet J.C.G., Cante-Barrett K., Pieters R., and Meijerink JPP. (2012). T-cell Acute Lymphoblastic Leukemia; A Roadmap to Targeted Therapies. *Blood Cancer Discov* 2 (1): 19–31. (Accessed 13 January 2012)

Coustan-Smith, E., Mullighan, C.G., Onciu, M. et al. (2009). Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. *Lancet Oncol* 10: 147–156.

Den Boer, M.L. et al. (2009). A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol* 10 (2): 125–134.

Gokbuget, N. (2021). MRD in adult Ph/BCR-ABL-negative ALL: how best to eradicate? *Hematol Am Soc Hemat Educ Prog* (1): 718–725.

Harvey R.C. and Tasian S.K. (2020). Clinical diagnostics and treatment strategies for Philadelphia chromosome-like acute lymphoblastic leukemia. *Blood Adv* 4 (1): 218–228. (Accessed 14 January 2020)

Hoelzer, D., Bassan, R., Dombret, H., Fielding, A., Ribera, J.M., and Buske, C. ESMO Guidelines Committee (2016 September). Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27 (suppl 5): v69–v82.

Hoelzer, D. (2017). Clinical Applications and pitfalls of MRD in ALL. *Clin Lymphoma Myeloma Leuk* 17: S9–S11.

Hoelzer, D., Thiel, E., Loffler, H. et al. (1988). Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood* 71 (1): 123–131.

Kimble E.L. and Cassaday R.D. (2021). Antibody and cellular immunotheripes for acute lymphoblastic leukemia in adults. *Leukemia & Lymphoma* 62 (14): 3333–33347.

Malard F. and Mohty M. (2020). Acute lymphoblastic leukaemia. *The Lancet* 395 (10230): 1146–1162.

Mullighan, C.G., Su, X., Zhang, J. et al., Children's Oncology Group (2009 January 29). Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med* 360 (5): 470–480.

Neumann, M., Heesch, S., Gökbuget, N. et al. (2012). Clinical and molecular characterization of early T-cell precursor leukemia: a high-risk subgroup in adult T-ALL with a high frequency of FLT3 mutations. *Blood Cancer J* 2 (1): e55.

Roberts, K.G., Li, Y., Payne-Turner, D. et al. (2014). Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 371 (11): 1005–1015.