

Preface

Acute Lymphoblastic Leukemia – Quo Vadis?



Meir Wetzler, MD, FACP Wendy Stock, MD
Guest Editors

Acute lymphoblastic leukemia (ALL) is one of the most challenging malignant diseases in adults with respect to the intricacies of clinical presentation, diagnosis, and treatment. This preface previews the articles that follow, touching on current treatment strategies for ALL, presenting the controversies regarding the role of allogeneic stem cell and bone marrow transplantation (BMT) for ALL in first remission, and concluding with a look toward the future and a discussion concerning new data about the leukemia stem cells (LSCs) in this disease and how this knowledge will lead to new therapeutic strategies.

CURRENT ACUTE LYMPHOBLASTIC LEUKEMIA TREATMENT

Table 1 outlines the current treatment approaches for adults with ALL. Many of these approaches have been adapted from the successful treatment regimens developed for children with this disease. The article by Pui and colleagues, elsewhere in this issue reviews in detail the state-of-the-art treatment strategies for children with ALL. The survivorship in pediatric ALL now exceeds 80%. As a result, pediatricians are now turning more of their attention to concerns about sequelae of their treatment, as discussed in the article by Nathan and colleagues, elsewhere in this issue.

Overall, the outcome in adults with either B-cell or T-cell ALL with any of the approaches outlined in **Table 1** results in approximately 30% to 40% 5-year survival.¹ The main achievements in the last few years have been the inclusion of imatinib mesylate (Gleevec) and other tyrosine kinase inhibitors in Philadelphia-positive ALL (see article by Ravandi and colleagues, elsewhere in this issue), the approval of nelarabine (Arranon) for T-ALL (see article by DeAngelo and colleagues, elsewhere in this issue), the pediatric approach to treat ALL in adolescents and young adults (see article by Ribera and colleagues, elsewhere in this issue), and the inclusion of anti-CD20

Characteristics	B	T	Ph+	Burkitt
Treatment	BFM-like regimen: Induction with VCR, PRED, daunorubicin, and L-ASP; Early intensification with CTX, ARA-C, 6-MP, VCR; Central nervous system prophylaxis with intrathecal MTX with either cranial irradiation or high-dose MTX and ARA-C; Late intensification with doxorubicin, VCR, DEXA, CTX, 6-TG and ARA-C; Maintenance with VCR, PRED, 6-MP and MTX to complete 24 months. Hyper-CVAD regimen: Alternating courses of CTX, VCR, doxorubicin and DEXA with MTX and high-dose ARA-C; Central nervous system prophylaxis includes intrathecal chemotherapy; Maintenance with VCR, PRED, 6-MP and MTX to complete 24 months.		Addition of imatinib to any of the approaches described for B-lineage diseases	CTX, VCR, doxorubicin, high-dose MTX and intrathecal therapy alternating with ifosfamide, VP-16, high-dose ARA-C, and intrathecal therapy
New aspects	Anti-CD20 Ab ^a ; different regimen for AYA ^d	Nelarabine ^b ; different regimen for AYA ^d	New TKIs ^c	Anti-CD20 Ab ^a

Abbreviations: Ab, antibody; ARA-C, cytosine arabinoside; AYA, adolescents and young adults; BFM, Berlin-Frankfurt-Münster; CTX, cyclophosphamide; CVAD, cyclophosphamide, vincristine, doxorubicin and dexamethasone; DEXA, dexamethasone; L-ASP, L-asparaginase; MTX, methotrexate; 6-MP, 6-mercaptopurine; PRED, prednisone; 6-TG, 6-thioguanine; TKI, tyrosine kinase inhibitors; VCR, vincristine; VP-16, etoposide.

^a See article by Thomas and colleagues, elsewhere in this issue.

^b See article by DeAngelo and colleagues, elsewhere in this issue.

^c See article by Ravandi and colleagues, elsewhere in this issue.

^d See article by Ribera and colleagues, elsewhere in this issue.

Data from Cavalli F, Hansen HH, Kaye SB, editors. The textbook of medical oncology, 4th edition. London: Informa Healthcare; 2009.

antibody into the ALL armamentarium (see article by Thomas and colleagues, elsewhere in this issue).

Two additional drugs are worth mentioning. One is pegylated asparaginase (Onco-spar), which decreases the immunogenicity of the enzyme, thus reducing the risk of hypersensitivity reactions.² Another advantage of pegylated asparaginase is its long half-life. Its use in adult ALL has been lagging behind its use in pediatric ALL because of lack of pharmacokinetic and pharmacodynamic data in adults. However, two recent publications may change this trend. Specifically, the demonstration of the safety of intravenous pegylated asparaginase during remission induction in adult ALL with favorable pharmacodynamics and decreased hypersensitivity reactions³ suggests that this route of administration will replace the intramuscular and subcutaneous routes. Furthermore, the findings that effective asparagine depletion with pegylated asparaginase resulted in improved outcome in adult ALL⁴ suggest that monitoring for asparagine depletion will become part of the treatment approach in these patients.

The second drug worth noting is clofarabine (Clolar), a novel deoxyadenosine analog with clinical activity in refractory and relapsed pediatric ALL (see article by Jeha and colleagues, elsewhere in this issue). Its role in combination with other drugs in relapsed/refractory adult ALL is being investigated.^{5,6} If efficacy of clofarabine combination therapy is identified in advanced stage ALL, it might be reasonable to explore the use of clofarabine as a front-line agent in adult ALL.

The concluding article by Abutalib and colleagues, elsewhere in this issue discusses other novel agents.

TO B(MT) OR NOT TO B(MT): A RISK-BASED DECISION

BMT is usually recommended to high-risk ALL patients in first remission and those in second and beyond remission. The recent Medical Research Council (MRC)/Eastern Cooperative Oncology Group (ECOG) trial⁷ suggested a benefit for sibling donor transplantation in standard-risk ALL in first remission without any significant benefit for high-risk ALL. Others challenge this recommendation.⁸ These data and the current controversies are reviewed elegantly in the article by Forman and colleagues, elsewhere in this issue and in the article by Ribera and colleagues, elsewhere in this issue. To understand the controversies about optimal treatment selection for adults with ALL reviewed in this issue, we highlight below some of the traditional and some of the newer biologic risk factors that prognosticate for treatment outcome in adult ALL.

The traditional ALL risk factors (high-risk factors denoted in parenthesis) are divided between the host and the disease.^{9,10} The host-related factors include age (>60) and performance status (poor), while the disease-related factors include white blood cell count ($>30 \times 10^9/L$ for B-cell ALL and $>100,000 \times 10^9/L$ for T-cell ALL), mediastinal mass (present), immunophenotype (B-cell), karyotype (t[9;22], +8, t[4;11], -7 and hypodiploid karyotypes) and lactate dehydrogenase (high level is associated with poor outcome and central nervous system disease). In addition, time to achieve complete remission (>4 weeks) is also recognized as a significant risk factor. Finally, the treatment team and the patient may also play a role in predicting outcome as it was recently implied that time to postremission treatment was an independent prognostic factor in adult ALL.¹¹ However, these traditional factors may not be sufficient to predict outcome of standard-risk ALL.

Recently, additional risk factors have been identified. The most important one on the host side is the presence of genetic variability in drug metabolism pathways.¹² Examples include 6-mercaptopurine, methotrexate, steroids, and asparaginase (see article by Abutalib and colleagues, elsewhere in this issue). On the disease side, novel

molecular markers were identified that help determine outcome. In T-cell ALL, high expression of *v-ets* erythroblastosis virus E26 oncogene homolog (avian) (ERG); brain and acute leukemia, cytoplasmic (BAALC)¹³; and T-cell leukemia homeobox 3 (TLX3)¹⁴ were associated with unfavorable outcome. In addition, expression of multi-drug resistance proteins in the leukemia blasts is associated with adverse outcome.¹⁵ Finally, presence of minimal residual disease was shown to adversely affect outcome in both pediatric and adult studies (see article by Campana and colleagues, elsewhere in this issue). These risk factors, however, are currently only available through select and meticulously conducted clinical trials in academic centers. As we begin to study the impact of these factors in prospective trials, we will undoubtedly obtain critical insights that may help to guide the recommendation for a stem cell transplant in first remission.

ACUTE LYMPHOBLASTIC LEUKEMIA STEM CELLS

Hematopoiesis is the highly orchestrated process of blood cell production by which the billions of white blood cells, red blood cells, and platelets lost daily are replaced to maintain homeostasis.¹⁶ Hematopoietic stem cells (HSCs) are the small population of long-lived, quiescent, undifferentiated, pluripotent cells characterized by a capacity of self-renewal, an exceptional proliferation potential, resistance to apoptosis, and the ability of multilineage differentiation into all types of blood cells mediated by the production of several lineage-committed progenitors.^{16–20}

The central role of LSCs in the pathogenesis of leukemias has become well recognized over the last 2 decades. LSCs share many of the basic characteristics with normal HSCs, including quiescence, self-renewal, extensive proliferative capacity, and the ability to give rise to differentiated progeny in a hierarchical pattern.^{21–27} Some scientists even view leukemia as a newly formed, abnormal hematopoietic tissue initiated by a few LSCs that undergo an aberrant and poorly regulated process of organogenesis analogous to that of normal HSCs.²⁸ The LSCs from different types of leukemias are likely to exhibit different biologic features, including survival and self-renewal pathways and immunophenotype.²⁹

Many researchers believe that the persistence of LSCs, which are resistant to most of the traditional chemotherapeutic agents that kill the bulk of the leukemic cell populations, is a major cause of leukemia relapse after “successful” induction of remission. Subsequently, designing effective therapeutic modalities that specifically target the LSC is likely to reduce the incidence of relapse, and even possibly lead to cure. The main question that remains unanswered nowadays is: What are the LSCs in ALL?

Due to the clear limitations of conducting controlled experiments on humans, most of our current knowledge about human LSCs was obtained indirectly from *in vitro* studies, xenotransplantation of human cells into immunodeficient animals, and transplant experiments involving primates and other large animals.¹⁶

The hypothesis that a subset of leukemia cells has distinct stem cell properties implies that LSCs arise as an inherent property of tumor biology and development.^{30,31} However, the bone marrow surroundings and the immune system offer support and are an intricate part of LSC survival and progression.³² One current controversy in the LSC arena concerns the intrinsic characteristic of LSCs in the experimental setting of xenotransplantation, where appropriate microenvironment features are missing because of differences between humans and mice.²⁴ This may have significant adverse effects on leukemic initiating capacity when these human LSCs are transplanted into nonobese diabetic (NOD)/severe combined immune-deficient (SCID)

mice.³³ Thus, LSCs that appeared to have failed transplantation may actually be fully leukemogenic in a microenvironmental setting with appropriate support.^{34,35}

Initially, it was reported that immature ALL stem cells capable of long-term proliferation *in vitro* and *in vivo* are CD34(+)/CD10(-)/CD19(-).³⁶ Similar data were reported with Ph(+) ALL cells.³⁷ However, recent reports demonstrated that more mature [CD34(+)/CD19(+)] ALL cells can initiate leukemia by xenotransplantation.^{38,39} These findings were associated with a switch to a more immune-deficient mouse strain, NOD/SCID/IL2r δ null.⁴⁰ This mouse has a mutation in the interleukin-2 receptor common gamma chain and is therefore devoid of not only T and B cells but also natural killer cells. Most recent twist to the theory of LSCs is the report that B precursor blasts in various stages of differentiation [CD34(+)/CD19(-), CD34(+)/CD19(+), CD34(-)/CD19(+)] displayed self-renewal capability, suggesting that leukemic lymphoid progenitors may not lose their self renewal capability with maturation⁴¹ or are able to “move backward” in differentiation.

This recent finding brings in the potential malleability or plasticity of LSCs. The term *plasticity* refers to the ability of organ-specific stem cells to recover their ability to differentiate into cells of other lineages, either *in vitro* or after transplantation *in vivo*.^{16,42,43} Here we use this term to describe the ability of more differentiated leukemic cells to reacquire the LSC characteristics. As a proof of concept, it was recently demonstrated that as few as 10 unselected ALL cells can initiate leukemia following xenotransplantation.⁴⁴

These findings may explain the poor outcome in ALL since any remaining blasts can theoretically “dedifferentiate” and start a progeny after “successful” achievement of remission. If indeed these cells can also regain the other LSC characteristics, such as multidrug resistance and resistance to apoptosis, better treatments targeting these cells are needed.

HSCs reside in the bone marrow, close to the endosteal surfaces of the trabecular bone in what is commonly referred to as *the niche*.⁴⁵ A stem-cell niche can be defined as a structure in which HSCs are housed for an indefinite period of time and maintained by allowing progeny production through self-renewal in the absence of differentiation.^{45–47} Several cell-surface receptors were implicated in controlling the localization of HSCs to the endosteal niche, among which is the chemokine receptor 4 (CXCR4). Its antagonist, AMD3100 (Mozobil) was recently approved as an HSC mobilizer before stem cell collection.⁴⁸

Somewhat promising in this regard is the recent demonstration of dependency on the stromal-derived growth factor 1 (SDF-1 α)/CXCR4 axis in Ph(+) ALL.⁴⁹ Specifically in this scenario, the Bcr-Abl kinase continued to be inhibited by imatinib, but the cells continued to proliferate in the presence of stromal support. The stromal effect did not require direct cell-cell contact and SDF-1 α substituted for the presence of the stromal cells. These data imply that the stroma-selected imatinib-resistant Bcr-Abl cells were less dependent on the kinase activity; thus, interrupting the interaction between the lymphoblasts and the stroma may be of benefit in Ph(+) ALL and most probably also in Ph(-) ALL. Initial studies demonstrating a role for AMD3100 in pediatric ALL⁵⁰ offer promise for the future about our ability to mobilize the remaining lymphoblasts from their niche and eradicate them.

SUMMARY

This issue attempts to answer the question: *Quo vadis?* Where are we going with respect to ALL treatment in both children and adults? While health care teams caring for children now focus on tailoring their successful therapies to minimize long-term

toxicities, those caring for adults are still working toward the goal of cure. The focus of therapy is increasingly based on the biologic characteristics of the patients. For one age group, adolescents and young adults, a pediatric approach seems warranted. However, this approach may be difficult to administer to older adults. This issue addresses current treatment strategies based on age and disease biology. The reader should be aware that the definition of “young” and “old” adults is in flux (ranging between 30 to 60 years old) and depends on the group (or the principal investigator) conducting the trial. The concluding article looks toward the future and reviews novel treatments that are moving into the clinic. Furthermore, we anticipate that that recent progress in our understanding LSC biology will shed light on the frequent relapses that occur after “successful” remission induction and will lead to therapeutic innovation and, ultimately, to the improved outcome of all patients with this challenging and heterogeneous disease.

ACKNOWLEDGEMENTS

The authors thank Dr. Hun J. Lee for his assistance preparing this preface.

Meir Wetzler, MD, FACP
Leukemia Section
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263, USA

Wendy Stock, MD
University of Chicago Hospitals and Cancer Research Center
5841 S. Maryland Avenue
Chicago, IL 60637, USA

E-mail address:
meir.wetzler@roswellpark.org (M. Wetzler)

REFERENCES

1. Larson S, Stock W. Progress in the treatment of adults with acute lymphoblastic leukemia. *Curr Opin Hematol* 2008;15:400–7.
2. Zeidan A, Wang ES, Wetzler M. Pegasparginase: where do we stand? *Expert Opin Biol Ther* 2009;9:111–9.
3. Douer D, Yampolsky H, Cohen LJ, et al. Pharmacodynamics and safety of intravenous pegasparginase during remission induction in adults aged 55 years or younger with newly diagnosed acute lymphoblastic leukemia. *Blood* 2007;109:2744–50.
4. Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. *Blood* 2007;109:4164–7.
5. Faderl S, Gandhi V, O'Brien S, et al. Results of a phase 1-2 study of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukemias. *Blood* 2005;105:940–7.
6. Karp JE, Ricklis RM, Balakrishnan K, et al. A phase 1 clinical-laboratory study of clofarabine followed by cyclophosphamide for adults with refractory acute leukemias. *Blood* 2007;110:1762–9.
7. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia (ALL) the greatest benefit is achieved from a matched sibling allogeneic transplant in first complete remission (CR) and an autologous

- transplant is less effective than conventional consolidation/maintenance chemotherapy in ALL patients: final results of the international ALL trial (MRC UKALL XII/ ECOG E2993). *Blood* 2008;111:1827–33.
8. Larson RA. Allogeneic hematopoietic cell transplantation is not recommended for all adults with standard-risk acute lymphoblastic leukemia in first complete remission. *Biol Blood Marrow Transplant* 2008;15:11–6.
 9. Hoelzer D, Thiel E, Loeffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood* 1988;71:123–31.
 10. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood* 1995;85:2025–37.
 11. Advani AS, Jin T, Ramsingh G, et al. Time to post-remission therapy is an independent prognostic factor in adults with acute lymphoblastic leukemia. *Leuk Lymphoma* 2008;49:1560–6.
 12. Cheok MH, Pottier N, Kager L, et al. Pharmacogenetics in acute lymphoblastic leukemia. *Semin Hematol* 2009;46:39–51.
 13. Baldus CD, Martus P, Burmeister T, et al. Low ERG and BAALC expression identifies a new subgroup of adult acute T-lymphoblastic leukemia with a highly favorable outcome. *J Clin Oncol* 2007;25:3739–45.
 14. Ballerini P, Landman-Parker J, Cayuela JM, et al. Impact of genotype on survival of children with T-cell acute lymphoblastic leukemia treated according to the French protocol FRALLE-93: the effect of TLX3/HOX11L2 gene expression on outcome. *Haematologica* 2008;93:1658–65.
 15. Swerts K, De Moerloose B, Dhooge C, et al. Prognostic significance of multidrug resistance-related proteins in childhood acute lymphoblastic leukaemia. *Eur J Cancer* 2006;42:295–309.
 16. Smith C. Hematopoietic stem cells and hematopoiesis. *Cancer Control* 2003;10:9–16.
 17. Szilvassy SJ. The biology of hematopoietic stem cells. *Arch Med Res* 2003;34:446–60.
 18. Wang JC, Dick JE. Cancer stem cells: lessons from leukemia. *Trends Cell Biol* 2005;15:494–501.
 19. Guo W, Lasky JL 3rd, Wu H. Cancer stem cells. *Pediatr Res* 2006;59:59R.
 20. Huang X, Cho S, Spangrude GJ. Hematopoietic stem cells: generation and self-renewal. *Cell Death Differ* 2007;14:1851–9.
 21. Terpstra W, Ploemacher RE, Prins A, et al. Fluorouracil selectively spares acute myeloid leukemia cells with long-term growth abilities in immunodeficient mice and in culture. *Blood* 1996;88:1944–50.
 22. Guan Y, Gerhard B, Hogge DE. Detection, isolation, and stimulation of quiescent primitive leukemic progenitor cells from patients with acute myeloid leukemia (AML). *Blood* 2003;101:3142–9.
 23. Guzman ML, Neering SJ, Upchurch D, et al. Nuclear factor-kappaB is constitutively activated in primitive human acute myelogenous leukemia cells. *Blood* 2001;98:2301–7.
 24. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med* 1997;3:730–7.
 25. Jordan CT. The leukemic stem cell. *Best Pract Res Clin Haematol* 2007;20:13–8.
 26. Jordan CT. Unique molecular and cellular features of acute myelogenous leukemia stem cells. *Leukemia* 2002;16:559–62.
 27. Jordan CT, Guzman ML. Mechanisms controlling pathogenesis and survival of leukemic stem cells. *Oncogene* 2004;23:7178–87.

28. Passegue E, Jamieson CH, Ailles LE, et al. Normal and leukemic hematopoiesis: are leukemias a stem cell disorder or a reacquisition of stem cell characteristics? *Proc Natl Acad Sci U S A* 2003;100(Suppl 1):11842–9.
29. Krause DS, Van Etten RA. Right on target: eradicating leukemic stem cells. *Trends Mol Med* 2007;13:470–81.
30. Dick JE. Stem cell concepts renew cancer research. *Blood* 2008;112:4793–807.
31. Bissell MJ, Labarge MA. Context, tissue plasticity, and cancer: are tumor stem cells also regulated by the microenvironment? *Cancer Cell* 2005;7:17–23.
32. Mantovani A. Cancer: Inflaming metastasis. *Nature* 2009;457:36–7.
33. Kelly PN, Dakic A, Adams JM, et al. Tumor growth need not be driven by rare cancer stem cells. *Science* 2007;317:337.
34. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57–70.
35. O'Brien CA, Pollett A, Gallinger S, et al. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature* 2007;445:106–10.
36. Cox CV, Evely RS, Oakhill A, et al. Characterization of acute lymphoblastic leukemia progenitor cells. *Blood* 2004;104:2919–25.
37. Cobaleda C, Gutierrez-Cianca N, Perez-Losada J, et al. A primitive hematopoietic cell is the target for the leukemic transformation in human philadelphia-positive acute lymphoblastic leukemia. *Blood* 2000;95:1007–13.
38. Castor A, Nilsson L, Astrand-Grundstrom I, et al. Distinct patterns of hematopoietic stem cell involvement in acute lymphoblastic leukemia. *Nat Med* 2005;11:630–7.
39. Hong D, Gupta R, Ancliff P, et al. Initiating and cancer-propagating cells in TEL-AML1-associated childhood leukemia. *Science*. 2008;319:336–9.
40. M Ito, Hiramatsu H, Kobayashi K, et al. NOD/SCID/gamma cnull mouse: an excellent recipient mouse model for engraftment of human cells. *Blood* 2002;100:3175–82.
41. le Viseur C, Hotfilder M, Bomken S, et al. In childhood acute lymphoblastic leukemia, blasts at different stages of immunophenotypic maturation have stem cell properties. *Cancer Cell* 2008;14:47–58.
42. Kondo M, Scherer DC, Miyamoto T, et al. Cell-fate conversion of lymphoid-committed progenitors by instructive actions of cytokines. *Nature* 2000;407:383–6.
43. Trounson A. Stem cells, plasticity and cancer - uncomfortable bed fellows. *Development* 2004;131:2763–8.
44. Morisot SWA, Bohana-Kashtan O, et al. Leukemia stem cell (LSC) are frequent in childhood precursor B acute lymphoblastic leukemia (ALL). *Blood* 2008;112.
45. Ohlstein B, Kai T, Decotto E, et al. The stem cell niche: theme and variations. *Curr Opin Cell Biol* 2004;16:693–6.
46. Spradling A, Drummond-Barbosa D, Kai T. Stem cells find their niche. *Nature* 2001;414:98–104.
47. Wilson A, Trumpp A. Bone-marrow haematopoietic-stem-cell niches. *Nat Rev Immunol* 2006;6:93–106.
48. Nervi B, Link DC, DiPersio JF. Cytokines and hematopoietic stem cell mobilization. *J Cell Biochem* 2006;99:690–705.
49. Mishra S, Zhang B, Cunnick JM, et al. Resistance to imatinib of bcr/abl p190 lymphoblastic leukemia cells. *Cancer Res* 2006;66:5387–93.
50. Juarez J, Dela Pena A, Baraz R, et al. CXCR4 antagonists mobilize childhood acute lymphoblastic leukemia cells into the peripheral blood and inhibit engraftment. *Leukemia* 2007;21:1249–57.