

Adult ALL: Where Are We and Where Are We Going?

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Could you provide some historical perspective on the treatment of adult acute lymphoblastic leukemia?

Adult acute lymphoblastic leukemia (ALL) is a relatively uncommon disease among young and middle-aged adults, although the incidence begins to rise again in older adults. The management of ALL in adults has followed the successes in the treatment of childhood ALL; adult oncologists have tried to transfer some of the same treatment approaches into adults. This strategy has met with mixed success, and while it has taken us to where we currently are, it seems unlikely to lead to further improvements. The limited effectiveness of these approaches in adult patients is due in part to the fact that adults, and particularly older adults, generally do not tolerate these therapies as well as children. This is certainly true for important ALL drugs such as vincristine and L-asparaginase. But more importantly, the varieties of ALL that are seen in adults are not the same as those seen in children. In adults, there are fewer, if any, cases of ALL with the *TEL-AML1* rearrangement, which is a very favorable subset of childhood acute myeloid leukemia (AML). There are also relatively few adults with chromosomal hyperdiploidy in ALL, which is another favorable subset in children. In contrast, approximately one quarter of the adult patient population has the 9,22 rearrangement that results in the Philadelphia chromosome (Ph). Until recently, that subtype of ALL has been quite resistant to conventional chemotherapy approaches.

Does adult ALL arise as a secondary leukemia?

There are not much data on adult ALL arising as a secondary malignancy. There are patients who develop ALL after exposure to chemotherapy for another disease, but this problem is less common than therapy-related AML. The etiology of the ALL cases that follow prior therapy has been less well clarified in terms of the leukemogenic drugs to which these patients have been exposed.

ALL as a second malignant disease may sometimes be part of a cancer syndrome, such as Li-Fraumeni syndrome. We

have seen a number of patients who, after treatment for a solid tumor cancer, developed ALL that was probably part of this syndrome.

Has standard chemotherapy been able to prolong survival in adult ALL patients?

Chemotherapy is very effective in inducing complete remissions in the adult ALL population, but only approximately 40% of patients are cured. Thus, these outcomes are quite different from those seen among children with ALL, for whom the long-term survival and cure rate is now 75–80%. The median survival reported for most series that include older adult patients is about 2 years.

How has the therapeutic approach for treating adult ALL been developed?

For the most part, chemotherapy drugs and treatment strategies that have been successful in children with ALL have been translated into the adult population. Most of the commonly used adult treatment programs were developed through single arm, phase II studies looking for improvements in outcome compared to historical results. There have been relatively few randomized, prospective clinical trials in adult ALL, in part because adult ALL is an uncommon disease with several different variants with different prognoses. In contrast, ALL has been a research priority for the pediatric oncology groups, and many important treatment issues have been evaluated in children in randomized trials around the world. Much of the progress made in recent years in adult ALL has been to delineate different risk groups based on characteristics such as age, white blood cell count at diagnosis, immunophenotype, and genotype.

Has transplantation been studied in adult ALL?

French investigators conducted the first large randomized trial focusing on stem cell transplantation in adult ALL. There is a very large study being done now by the Medical Research Council in the United Kingdom and the Eastern Cooperative Oncology Group in the US in which adults

with ALL who have a sibling donor available are assigned to have an allogeneic transplant in first remission. All other patients are randomly assigned to continue chemotherapy or to undergo autologous transplantation. The preliminary data from this study do not yet support allogeneic transplantation as a universally better treatment approach than intensive postremission chemotherapy. However, there are subsets of adult ALL where transplantation is clearly able to cure patients who are not curable with conventional chemotherapy. These subsets include Ph(+) patients, and probably patients with the 4,11 translocation. These 2 groups have not done well with conventional chemotherapy, and it has been generally recommended that they undergo an allogeneic transplant early in first remission if they have a donor available, either a sibling or a matched unrelated donor. In addition, any patient who relapses despite an intensive frontline chemotherapy program should be considered for allogeneic transplantation.

There has not been as much information on autologous transplantation studies in ALL. It does not appear that autotransplantation by itself is better than intensive postremission chemotherapy. The incorporation of imatinib into transplantation regimens for patients with Ph(+) ALL is currently being explored for those patients who do not have an allogeneic donor. Autologous stem cells that are *BCR/ABL(-)* are collected from patients who received imatinib after achieving an initial response in order to test the effectiveness of autotransplantation in that subset.

How is imatinib being incorporated into the treatment of adult ALL?

Imatinib (Gleevec, Novartis) is an important drug in the treatment of Ph(+) ALL, although it is unlikely to benefit other subtypes of ALL. In the initial studies using single-agent imatinib for ALL patients with relapsed Ph(+) disease, a considerable fraction of patients achieved a complete remission. However, these remissions tended to be quite short, lasting only a couple of months in most cases. If such a patient had not undergone transplantation in their first remission, then single-agent imatinib could be an effective preparation for relapsed patients prior to transplantation.

Current clinical trials for adult Ph(+) ALL are incorporating imatinib into the treatment plan in 1 of 3 ways. Dr. Deborah Thomas and colleagues at the University of Texas M. D. Anderson Cancer Center have administered imatinib concurrently with chemotherapy during the remission induction and postremission therapy. The early reports from this study thus far show that the combination appears to be well tolerated with no additional toxicity, and that the addition of imatinib increases the effectiveness of induction chemotherapy so that most patients will achieve a complete remission. This approach has enabled a greater fraction of patients to proceed directly to an allogeneic transplant. Somewhat disappointing is the fact that despite the high response rate and the ability to transplant more of these patients, there have still been a number of relapses reported in this series. The Japanese ALL Study

Group has also successfully combined imatinib with conventional ALL chemotherapy for Ph(+) ALL.

The Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group are conducting a collaborative trial using conventional induction chemotherapy followed by imatinib as a single agent in high doses as immediate postremission therapy. This sequential approach is then followed by either an allogeneic or autologous transplant.

Imatinib is also being studied as single-agent induction therapy in older patients who otherwise would tolerate remission induction therapy poorly. This study is being conducted by the German Multicenter ALL Study Group, which has reported a high response rate and excellent tolerance in older, Ph(+) patients who were given single-agent imatinib for induction. However, postremission therapy appears important to prevent early relapses.

Are there other targeted types of therapy being studied in ALL?

Imatinib is the only tyrosine kinase inhibitor currently being studied for adult ALL. Flt3 inhibitors are being considered as a potential therapeutic approach. While activating mutations in the Flt3 receptor are not common in ALL, it appears that many ALL blasts overexpress this gene product.

Several monoclonal antibodies are currently being evaluated in clinical trials. Rituximab (Rituxan, Genentech), an anti-CD20 antibody, is being investigated at the University of Texas M. D. Anderson Cancer Center for patients with precursor B-cell ALL that expresses CD20. This subset comprises approximately one quarter of patients with ALL.

The CD33 antigen is also being studied as a potential therapeutic target. Although only 5–10% of ALL blasts aberrantly express CD33, investigators are considering this approach with gemtuzumab ozogamicin (Mylotarg, Wyeth), which targets this antigen and has been approved for treating CD33(+) AML.

Finally, the CD52 antigen is being explored as a potential target for alemtuzumab (Campath, Berlex). Reports have noted that this antigen is expressed on approximately 70% of all ALL cells—more commonly on precursor B-cell blasts than on T-cell blasts. The CALGB is currently accruing patients to a trial that uses conventional chemotherapy for remission induction and consolidation, followed 3 months later by alemtuzumab, given at the time of minimal residual disease. This approach may minimize toxicity and simultaneously exploit any antileukemic activity that the antibody has against residual lymphoblasts.

What is currently understood about the causes of adult ALL?

We do not understand much about the causes of adult ALL. It is not likely that the data on the genesis of infant ALL as occurring in the fetus will be relevant in adult ALL. Similarly, the exposure or lack of exposure to childhood illnesses that may play a role in the etiology of ALL

in childhood is not likely to be relevant to ALL in older adults. The possible causes of Ph(+) ALL are not clear at all. This disease subset, which is uncommon in children, accounts for nearly half of all ALL patients over age 60.

Where is the field going and where do you think it needs to go?

While dose escalations and other intensive induction regimens continue to be studied, it is unlikely that treatment with conventional chemotherapy drugs alone will improve outcomes beyond their current status. There is a critical need to introduce new agents into the treatment of ALL. Imatinib will be an important advance in the treatment of Ph(+) patients, the most difficult subset to treat. Whether the monoclonal antibodies now being studied will provide any additional benefit for other types of precursor B-cell ALL is not yet clear. Nelarabine (GlaxoSmithKline), once known as 506U78, is a recently developed agent that has shown considerable activity in children and adults with relapsed T-cell ALL and now needs to be evaluated in newly diagnosed T-cell ALL patients.

Adult oncologists who treat a broad spectrum of cancers often lack the special expertise that pediatric oncologists have in treating patients with ALL. Two recent reports have suggested that adolescents with ALL—that is, patients between the ages of 15 and 21—have had better outcomes when treated in pediatric centers rather than in adult cooperative group trials. The CALGB and Southwest Oncology Group are now designing a study in collaboration with the Children's Oncology Group that will focus specifically on adolescent ALL in order to understand better the determinants of outcome in this particular age group.

It is important to recommend that patients enroll in cancer center or cooperative group clinical trials so that different strategies can be studied prospectively. I believe that there is reason to be optimistic about improving the overall cure rate of adult ALL beyond the current 40%.

Does the identification of genetic subsets have an important role in the future of ALL treatment?

As flow cytometry and immunophenotyping have improved and become more widely available, the diagnosis of ALL has become much more straightforward. It is clear that ALL is made up of a number of different variants

of disease. Some of these variants, such as T-cell ALL or Burkitt leukemia/lymphoma, can be recognized by immunophenotyping. The identification of cytogenetic and molecular genetic subsets has rapidly progressed over the past several years, and important differences in outcomes according to genetic profile have been identified. Gene profiling is enabling identification of additional targets for the development of new therapies. It is likely that treatment advancements will be made against individual subsets. Progress would be made more quickly if there were increased participation in clinical trials that include as a key objective a better understanding of the molecular basis of this disease.

Suggested Reading

Kebriaei P, Larson RA. Progress and challenges in the therapy of adult acute lymphoblastic leukemia. *Curr Opin Hematol.* 2003;10(4):284-289.

Ferrando AA, Neuberg DS, Dodge RK, et al. Prognostic importance of *TLX1 (HOX11)* oncogene expression in adults with T-cell lymphoblastic leukaemia. *Lancet.* 2004;363:535-536.

Kebriaei P, Anastasi J, Larson RA. Diagnosis and classification of ALL. In: Dieter Hoelzer D and Goekbuget N, eds. *Acute Lymphocytic Leukemia.* 15(4): Bailliere's Best Practice and Research: Clinical Hematology. Exeter, UK: Elsevier Science; 2003:597-621.

Wassmann B, Pfeifer H, Scheuring UJ, et al. Early prediction of response in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) treated with imatinib. *Blood.* 2004;103(4):1495-1498.

Thiebaut A, Vernant JP, Degos L, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation. A follow-up report of the French protocol LALA 87. *Hematol Oncol Clin North Am.* 2000;14(6):1353-1366.

Lee S, Kim DW, Kim YJ, et al. Minimal residual disease-based role of imatinib as a first-line interim therapy prior to allogeneic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood.* 2003;102(8):3068-3070.

Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood.* 2003 Oct 9 [Epub ahead of print].

Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J Clin Oncol.* 2003;21(5):760-761.