SOHO Supplement 2016

Perspectives and Future Directions for Acute Lymphoblastic Leukemia

Anjali S. Advani

Clinical Practice Points

- Acute lymphoblastic leukemia (ALL) is a difficult disease to treat and novel therapies are needed. The Philadelphia (Ph)-like signature has recently been identified in ALL and portends a poor prognosis.
- Various fusion genes have been identified in Ph-like ALL and these may represent "drug-able" targets. Minimal residual disease is important prognostically and should be used routinely to guide clinical care.
- The incorporation or novel agents into upfront treatment is ongoing and should improve the prognosis of patients.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. S1, S6-9 © 2016 Elsevier Inc. All rights reserved.
Keywords: Antibody, Minimal residual disease, Novel therapies, Ph-like signature

I will begin with a patient case to highlight some of the major points I will be making. The patient was a 22-year-old man with relapsed precursor B (pre-B) acute lymphoblastic leukemia (ALL) who had presented to my clinic for possible participation in clinical trial S1312: a phase I trial of inotuzumab combined with CVP (cyclophosphamide, vincristine, prednisone). He was diagnosed in July 2012. At that time, fluorescence in situ hybridization studies demonstrated deletion of the *Ikaros* gene. He was treated with the pediatric-based regimen, C10403.[1] The patient developed a relapse 10 months after diagnosis and underwent salvage treatment with hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone). He achieved a complete remission (CR) and proceeded to double umbilical cord transplantation. The testing for minimal residual disease (MRD) after allogeneic transplantation was positive, and he developed a relapse approximately 1 year later. At his consultation with me, repeat bone marrow testing demonstrated the presence of the *CRLF2* rearrangement (Philadelphia [Ph]-like signature).

Determining Molecular Features Predictive of Relapse and Incorporating Targeted Therapy Upfront

The presented case illustrates the importance of determining the molecular features predictive of relapse and attempting to incorporate targeted therapy upfront. For patients with acute myeloid leukemia, we routinely use molecular markers for risk stratification and treatment. For example, in patients with normal cytogenetics, we check for nucleophosmin, FLT3, and CEBP-α. In ALL, until recently, we have mainly been evaluating the Ph chromosome (*Bcr-Abl*) and the mixed lineage leukemia gene (*MLL*). In Ph^+ ALL, the incorporation of tyrosine kinase inhibitor therapy into upfront treatment has markedly improved the outcomes.

Our patient had deletion of *Ikaros* and presence of the Ph-like signature. Children with ALL and the Ph-like signature have an extremely poor clinical outcome (Figure 1).[2] The incidence of this signature is greater (20%-25%) in young adults, and the Children's Oncology Group has developed an assay to identify this signature.[2] This signature clearly predicts for inferior event-free and overall survival. Therefore, the question is whether targeting this signature can improve outcomes, similar to Ph^+ ALL. Patients with the Ph-like signature have various kinase fusions. These fusions retain intact tyrosine kinase domains, and the incidence of these various fusions differs with age (Figure 2).[3] Future laboratory correlates in clinical trials E1910 and S1318 will help better characterize these fusions in adults and older adults. More than 100 in-frame fusions have been identified, with 32 involving 12 tyrosine kinase or cytokine receptor genes.[3] Many of these fusions have a "drug-able" target. For example, in our patient with a *CRLF2* fusion, JAK2 inhibitors have demonstrated activity.[4] Therefore, a study has been developed within the Children's Oncology Group (Figure 3) to identify and treat these patients upfront. Patients with high- and standard-risk pre-B ALL can be enrolled in study AALL1131. They receive a 4-drug induction, and at study entry, testing is sent for the Ph-like signature. Patients with a Ph-like dasatinib-sensitive kinase mutation are then treated with dasatinib combined with chemotherapy. The hope is that such an approach will improve outcomes for these patients.

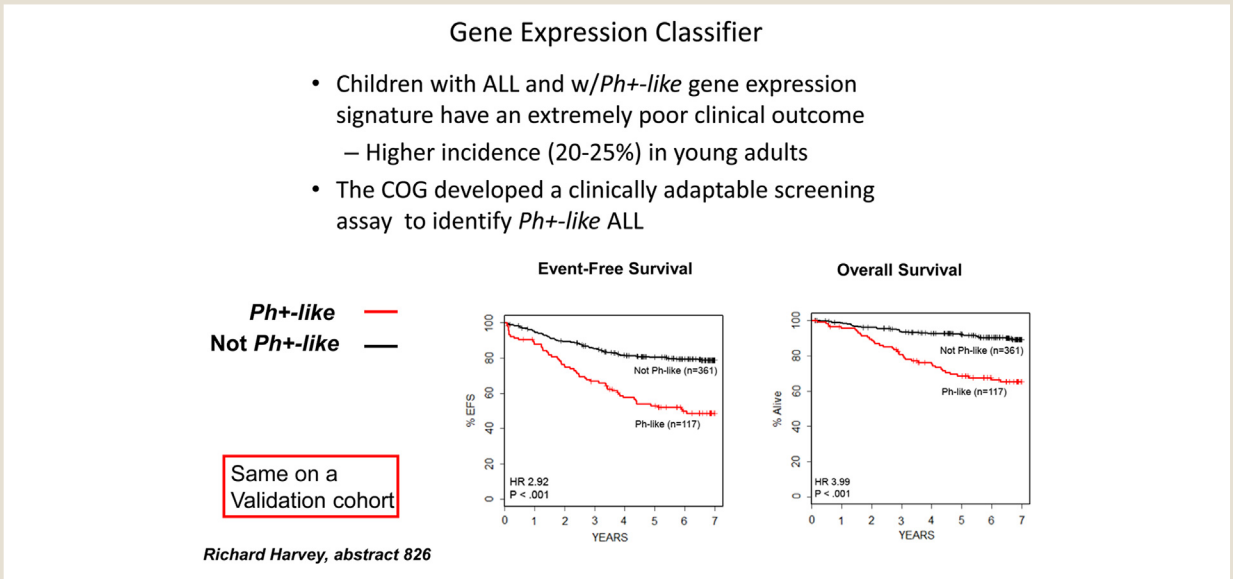
Department of Hematology/Oncology, Cleveland Clinic, Cleveland, OH

Submitted: Feb 9, 2016; Accepted: Feb 9, 2016

Address for correspondence: Anjali S. Advani, MD, Desk R35, 9500 Euclid Avenue Cleveland Clinic, Cleveland, OH 44195
E-mail contact: advania@ccf.org

2152-2650/$ - see frontmatter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2016.02.030

Figure 1 The Outcome of Young Adults With Philadelphia (Ph)-Like Acute Lymphoblastic Leukemia (ALL)



Abbreviations: COG = Children's Oncology Group; HR = hazard ratio.

Figure 2 (A) Examples of Kinase Fusions Seen in Philadelphia-Like Acute Lymphoblastic Leukemia (ALL). (B) Incidence of Kinase Fusions in Various Age Groups (Reprinted courtesy of Kathryn Roberts)