SOHO State of the Art Updates and Next Questions

Philadelphia Chromosome–like Acute Lymphoblastic Leukemia

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Abstract

Philadelphia chromosome–like acute lymphoblastic leukemia (Ph-like ALL) is a recently described B-cell precursor ALL with a gene expression profile and a high frequency of *IKZF1* gene alteration similar to that of Ph-positive ALL. Its prevalence is approximately 12% in children, 21% in adolescents (16-20 years of age), and 20% to 24% in adults older than 40 years, with a peak (27%) in young adults 21 to 39 years old. It occurs more often in male individuals and patients with Down syndrome. Ph-like ALL is overrepresented in those with Hispanic ethnicity and is associated with inherited genetic variants in *GATA3* (rs3824662). It is a clinically and biologically heterogeneous subtype of B-ALL. Although most patients with Ph-like ALL have positive minimal residual disease after remission induction and poor event-free survival, approximately 40% of pediatric patients responded well to chemotherapy and can be cured with relatively low intensity of treatment. The treatment outcome correlated negatively with increasing age at presentation. Ph-like ALL is characterized by a wide range of genetic alterations that dysregulate several cytokine receptor and kinase signaling pathways, including *CRLF2* rearrangement in half of the cases and translocation of nonreceptor tyrosine kinases (predominantly ABL-class and Janus kinases). Patients with ABL-class fusions respond clinically to ABL1 tyrosine kinase inhibitors, whereas mutations activating the JAK-STAT pathway are amendable to treatment with JAK inhibitors in vitro or in preclinical models. Prospective studies are needed to determine if incorporation of tyrosine kinase inhibitor targeting kinase alterations into intensive chemotherapy regimens will improve outcome of patients with Ph-like ALL.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 17, No. 8, 464-70
Keywords: BCR-ABL-like, *IKZF1* gene alteration, JAK inhibitors, Targeted therapy, Tyrosine kinase inhibitors

Introduction

Based on gene expression profiling studies of B-cell precursor ALL (B-ALL), Philadelphia chromosome (Ph)-like (also known as *BCR-ABL1*-like) acute lymphoblastic leukemia (ALL) was independently identified by 2 groups of investigators in 2009: the Children's Oncology Group (COG)-TARGET-St. Jude consortium and the Dutch Childhood Oncology Group.[1,2] This subtype of B-ALL has a gene expression profile similar to that of Ph-positive ALL but lacks the BCR-ABL1 fusion protein expressed from t(9;22)(q34.1;q11.2), and was associated with unfavorable clinical outcome when treated with conventional chemotherapy.[1,2] Like Ph-positive ALL,[3] Ph-like ALL cases also have a high frequency of genetic alterations of *IKZF1*, which encodes the lymphoid transcription factor Ikaros.[1,2] Such alterations are associated with poor outcome in both Ph-positive and Ph-negative ALL,[4] in part by dysregulating adhesion of and mislocalizing leukemic cells in the bone marrow niche.[5] All subsequent pediatric and adult studies have shown that this subtype of ALL is associated with dismal outcome,[6-13] with the exception of St. Jude Total Therapy Study XV, which was the first clinical trial to use minimal residual disease (MRD) levels prospectively during and after remission induction therapy to guide risk-directed treatment, which attenuated the poor prognosis of Ph-like ALL despite its association with high MRD levels[14] (Table 1). We here review the recent advances in the clinical and biologic studies that can be used to improve outcome of this high-risk genetic subtype of ALL.

Definition

Unlike Ph-positive and other genetic subtypes of ALL classified by nonrandom chromosomal translocations or gene fusions, Ph-like ALL is defined by gene expression profile and represents a more genetically heterogeneous disease. In fact, the 2 initial gene expression signatures used to make the original discovery identify an

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Submitted: Mar 24, 2017; Accepted: Mar 24, 2017

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2017.03.299

Table 1 Prevalence and Treatment Outcome of Philadelphia Chromosome-like ALL by Age Group

Clinical Trial	Age, y	Risk Group	Ph-like ALL Prevalence, (%)	n	Treatment Outcome		Reference
P9906	1-18	High-risk	31	68	5-y EFS	25.9% ± 10%	Mullighan[1]
COALL 92/97	0-18	All	19	28	5-y DFS	59.5%	Den Boer[2]
DCOG-ALL-8/9	0-18	All	15	10	5-y DFS	57.1%	Den Boer[2]
AALL0232	1-18	High-risk	14	81	5-y EFS	62.6% ± 6.9%	Loh[6]
DCOG-ALL-8/9/10	1-18	All	16	94	5-y CIR	32%	van der Veer[7]
Multiple trials							Roberts[8]
	1-15	Standard-risk	10	33	—	—	
	1-15	High-risk	12.7	108	5-y EFS	58.2% ± 5.3%	
	16-20	All	20.6	77	5-y EFS	41.0% ± 7.4%	
	21-39	All	27.4	46	5-y EFS	24.1% ± 10.5%	
HOVON	16-71	All	17	21	3-y EFS	~25%	Boer[9]
GMALL	15-65	All	13	26	5-y DFS	24%	Herold[10]
University Pennsylvania							Tasian[11]
	18-39	All	25.9	7	—	—	
	40-88	All	18.3	11	—	—	
Multiple trials							Roberts[12]
	21-39	All	27.9	96	5-y EFS	24.1%	
	40-59	All	20.4	62	5-y EFS	21.4%	
	60-86	All	24	36	3-y EFS	8%	
MD Anderson	15-84	All	33.1	49	5-y OS	23%	Jain[13]
St. Jude Total XV	1-18	All	11.6	40	5-y EFS	90.0% ± 4.7%	Roberts[14]

Abbreviations: AALL = acute lymphoblastic leukemia trial; CIR = cumulative risk of relapse; COALL = German Cooperative Acute Lymphoblastic Leukemia; DCOG = Dutch Childhood Oncology Group; DFS = disease-free survival; EFS = event-free survival; HOVON = Hematology-Oncology Foundation for Adults in the Netherlands; OS = overall survival.

overlapping, but not identical, subset of cases.[1,2,15] The COG-TARGET-St. Jude consortium first identified a subset of *IKZF1*-altered, high-risk B-ALL cases with a gene expression profile similar to Ph-positive ALL using Gene Set Enrichment Analysis,[1] and subsequently used prediction analysis of microarrays of Affymetrix gene expression microarray data of high-risk B-ALL to identify 257 gene probe sets that defined Ph-positive and Ph-like cases.[16] Genetic alterations deregulating cytokine receptor and tyrosine kinase genes, and deletions or mutations of the lymphoid transcription factor gene *IKZF1* (encoding Ikaros) are a hallmark of the subtype defined by this classifier. By contrast, the signature of Den Boer et al[2] was based on hierarchical clustering of 110 probe sets identified to predict other major pediatric ALL subtypes (T-cell, *ETV6-RUNX1*, high hyperdiploid, *TCF3-PBX1*, *MLL*-rearranged, and *BCR-ABL1*). Ph-like ALL defined by this signature had frequent deletions in B-cell development genes (eg, *IKZF1*), dic(9;20), and intrachromosomal amplification of chromosome 21.[2,7,15] Both signatures identified molecularly distinct but overlapping groups of patients with poor prognosis, but shared only 9 overlapping probe sets of 7 genes (*CCND2*, *SH3BP5*, *ABL1*, *SOCS2*, *DUSP6*, *LST1*, *EGFL7*).[15] Importantly, tyrosine kinase fusion genes involving *ABL1*, *PDGFRB*, and *JAK2* were found only in patients with Ph-like ALL using the classifier of COG-TARGET-St. Jude consortium.[15] Subsequently, the COG have developed a targeted low-density array that quantitates expression of 8 to 15 genes that are overexpressed in Ph-like ALL.[12] These probe sets, and the statistical algorithm used to convert raw gene expression data into a single numerical score predictive of Ph-like ALL, were selected and derived using large cohorts of cases with comprehensive genomic characterization. Thus, different clustering, prediction, and quantitative polymerase chain reaction (PCR) approaches have been used that result in inconsistent predictions, and this may result in confusion regarding the optimal approach to identify patients with Ph-like ALL. It is emphasized that the most consistent, robust predictions are obtained when gene expression prediction approaches are trained and applied using data from the same center and technical platforms; and that the approaches used must be shown to sensitively and reproducibly identify all kinase-activating alterations in Ph-like ALL.

Prevalence and Clinical Features

The prevalence of Ph-like ALL differs by age, gender, race, ethnicity, and National Cancer Institute (NCI)-defined risk groups. It comprises approximately 12% of children with B-cell precursor ALL (10% of NCI standard-risk and 13%-14% of NCI high-risk B-ALL), 21% of adolescents 16 to 20 years old, 27% of young adults 21 to 39 years old, and 20% to 24% of adults older than 40 years[8,11-13] (Table 1). Compared with Ph-positive ALL, the prevalence of Ph-like ALL is 3 to 4 times more common in children and approximately the same as that in adults. A higher proportion of patients with Ph-like ALL are male patients compared with those with non–Ph-like B-ALL in both children and adults with a male-to-female ratio of 2.0:1.0 and 1.6:1.0, respectively.[8,12,14] Hispanic patients have been shown to have a higher prevalence of Ph-like ALL, with a particular preponderance of *CRLF2* rearrangements.[13,17] This is in part explained by the higher frequency of germline Ph-like ALL risk variant in *GATA3* (rs3824662) in Hispanic individuals with Native American genetic ancestry.[18] This