Philadelphia-Like Acute Lymphoblastic Leukemia: A Systematic Review

Vineeta Yadav,[1] Prasanth Ganesan,[2] Raveendranath Veeramani,[1] Dinesh Kumar V[1]

Abstract

Philadelphia-like (Ph-like) acute lymphoblastic leukemia (ALL) is a subgroup of B-cell precursor ALL (BCP-ALL) with a gene expression profile analogous to Philadelphia-positive ALL and recurrent *IKAROS* Family Zinc Finger 1 (*IKZF1*) gene deletion despite lacking *BCR-ABL1* (Breakpoint cluster region-ABL protooncogene) translocation. Although recognized to occur at all ages, the proportion of cases among BCP-ALL varies (< 10% in children and up to 30% in adolescents). In all age groups, males are more commonly affected. Generally, Ph-like ALL is associated with adverse clinical features and an increased risk of treatment failure with conventional approaches. Genetic alterations such as aberrant expression, point mutations, or fusion translocations lead to activation of cytokine receptors and signaling kinases, which affect the *ABL1* (*ABL* class fusion) or Janus Kinase (*JAK*) signaling pathways. Several clinical trials are being conducted to understand whether specific tyrosine kinase inhibitor therapy can improve cure rates. This review summarizes the current literature available about this entity.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in the pediatric population, accounting for 25% of cancers diagnosed in this group.[1] ALL is characterized by the accumulation of malignant, immature lymphoid progenitor cells in the bone marrow, peripheral blood, and other sites, such as the lymph nodes, spleen, liver, and central nervous system.[1] Based on their origin from stem cell/progenitor cells, 2 common subtypes can be classified, namely: B-lineage ALL (B-ALL) and T-lineage ALL (T-ALL).[1] Recently, a new subgroup of B-ALL has been identified with a gene expression profile (GEP) that is similar to Ph-positive (Ph^+) ALL but with a myriad group of genetic alterations. This entity, however, lacks the t(9;22) translocation or the *BCR-ABL* fusion, and hence has been termed "Ph-like" ALL or "*BCR-ABL*-like" ALL.[2] These cases are frequently associated with the deletion of *IKZF1*. It has been reported by the previous studies that this particular subgroup is also associated with an inferior outcome, adverse clinical features, and treatment failure identical to Ph^+ ALL.[3]

We conducted a systematic review to understand the incidence, distinctive clinical features, and associated gene signatures of Ph-like ALL, and explore the outcomes of these patients with Ph-like ALL with current treatment.

Methods

Data Origins and Findings

For this review article, the investigators collected articles written in English from databases such as PubMed and Google Scholar, published from 2000 to 2019. The search for articles was done from March 15, 2019 to May 20, 2019. To fine-tune the search, keywords such as "B-ALL," "Acute lymphoblastic leukemia," "*BCR-ABL1*," "*CRLF2*," "interleukin-7 receptor," "Janus kinase 2," "Philadelphia-like ALL," "*IKZF1*," "*IKAROS*," and "MRD" were used. Papers were carefully assessed and classified based on inclusion and exclusion criteria. The citations for all databases were specified. This study was conducted based on the Preferred Reporting Items for Systematic Reviews (PRISMA) format.

Selection Criteria and Data Extraction

Studies of ALL that were either prospective or retrospective with the primary outcomes of our interest (incidence, diagnostic approach, prognostic impact, and several associated gene signatures of Ph-like ALL) were chosen. Data for the secondary outcome of

[1]Department of Anatomy
[2]Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

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Address for correspondence: Raveendranath Veeramani, MD, Department of Anatomy, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India 605006
E-mail contact: dr_raveendra@rediffmail.com

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interest, that is treatment targets of patients with Ph-like ALL, were extracted and reported for additional analysis.

The following studies were excluded: (1) studies of leukemias other than B-ALL; (2) lack of description about Ph-like ALL diagnosis incidence, treatment outcome, and survival rate; and (3) poor description of the applied methods.

Results

Search Outcome

The search process was concluded by analyzing abstracts of those articles fulfilling the inclusion criteria with primary and secondary outcomes. Then the patient sample, sample size, population ethnicity, methodology, and technical procedures were recorded. The initial evaluation resulted in the identification of 127 articles related to ALL. Of these 127 articles, 78 were excluded, and 50 were selected for full-length review. Thirty-one articles that lacked information related to baseline characteristic parameters were eliminated from the study in the second round of the selection process.

In the next stage, the selected articles were classified based on the incidence, distinctive clinical features, several associated gene signatures of Ph-like ALL, and the treatment protocols. The extracted information included the type of study, sample size, major findings, minimal residual disease (MRD) status, and survival outcome in both children and adolescent and young adult patients. The selection process is depicted in the form of a PRISMA flow diagram (Figure 1). The incidence and outcomes are tabulated based on the age group and method of analysis in Table 1. Table 2 contains the treatment outcomes in the 3 age groups studied in various clinical trials. Table 3 contains a description of altered kinase genes detected in Ph-like ALL. The algorithm for testing Ph-like ALL is described in Figure 2.

Baseline Characteristics of Included Studies

As seen in Table 4, the accumulation of 19 included studies rendered us the dataset of 12,973 patients with ALL and 1744 patients with Ph-like ALL. The median age of the patients in these studies ranged from 5.3 to 40 years, and the median white blood cell count ranged from 7.1 to 92.7 $\times$ 10^9/L. The methods used to diagnose the Ph-like ALL cases in these studies were predominantly prediction analysis for microarrays of an Affymetrix gene

Figure 1 Flow Diagram according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Format

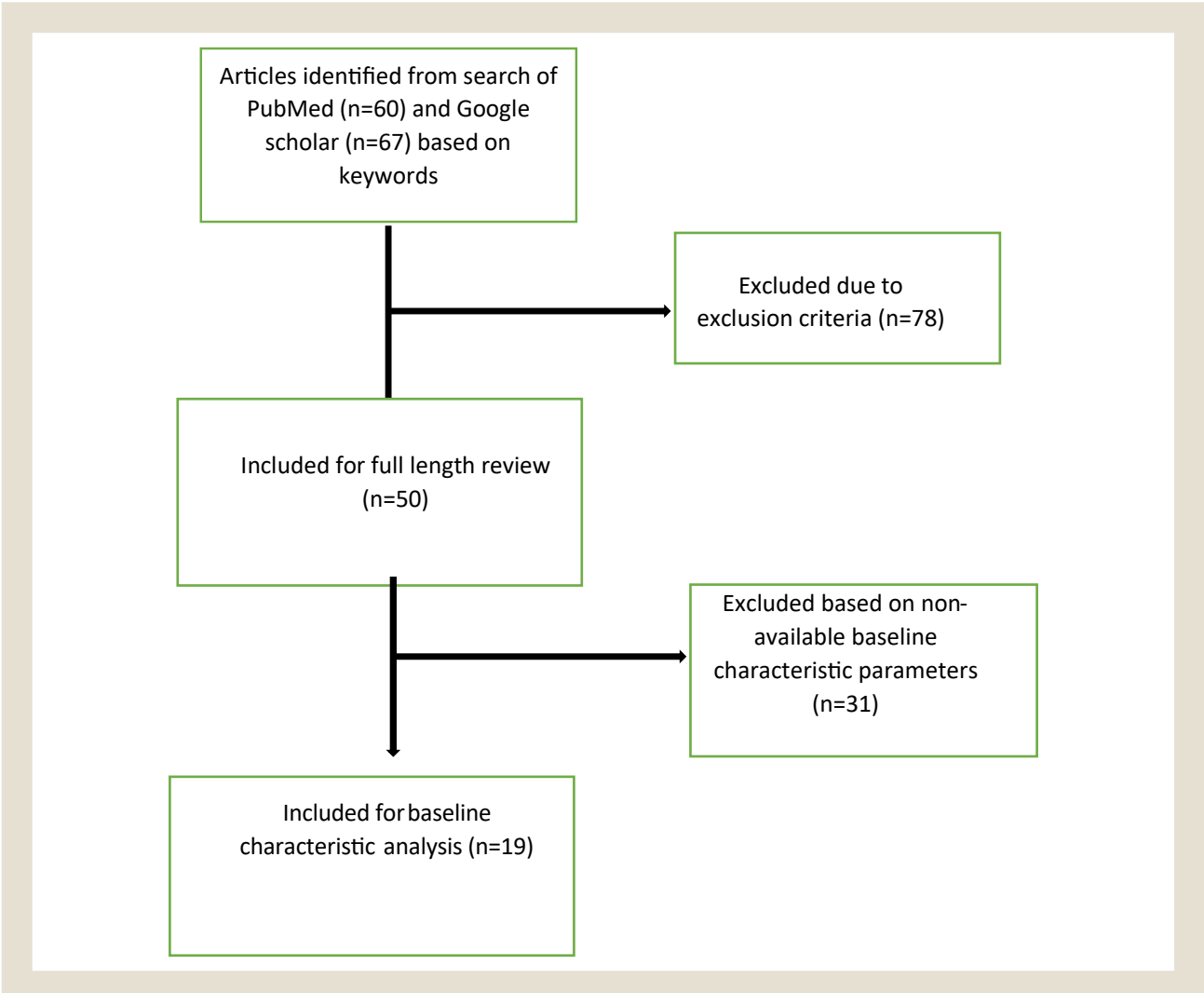


Table 1 Frequency and Outcomes of Ph-like ALL in Children, Adolescents, and Adults

Study	Age, y	Total No. B-ALL	No. Ph-like	Frequency Ph-like, %	Diagnostic Approach
Jain et al[4]	15-39	80	33	42	Gene expression profile, FISH
	40-84	68	16	24	
Herold et al[5]	16-20	26	5	19	Gene expression profile, FISH
	21-39	68	12	18	
	40-55	45	4	9	
	55-84	67	5	7	
Boer et al[6]	16-20	24	6	25	Gene expression signature
	21-39	48	9	19	
	40-71	55	6	11	
Roberts et al[7]	21-39	344	96	28	Genomic profiling, Transcriptome sequencing
	40-59	304	62	20	
	60-86	150	36	24	
Roberts et al[8]	1-15	853	108	13	Next-generation sequencing Microarray profiling and cytogenetic assays
	16-20	372	77	21	
	21-39	168	46	27	
Loh et al[9]	1-31	572	81	14	Gene expression profiles
Reshmi et al[10]	1-31	1389	284	20	Gene expression profile

Abbreviations: B-ALL = B cell acute lymphoblastic leukemia; FISH = fluorescence in situ hybridization; Ph-like ALL = Philadelphia-like acute lymphoblastic leukemia.

expression array based on 257 gene probe set, which was used in 11 studies.[3-5,7-9,14,15,17,20,21] Three studies used the hierarchical clustering of an Affymetrix gene expression array based on a probe set of 110 genes.[2,6,12] One study used the Xenograft model.[16]

Discussion

Molecular Characterization of Ph-Like ALL

Philadelphia-like ALL has a diversified genomic outlook in wide comprehensive genomic profiling studies, presenting with multiple rearrangements, copy number alterations, and sequencing, which leads to activation of tyrosine kinase or cytokine receptor signaling pathways.[7,8,10] To date, 60 rearrangements in 15 kinase or cytokine receptor genes have been documented.[3,7,8,10] Based on the activation of tyrosine kinase and cytokine receptor signaling pathway, these alterations can be categorized as 6 confined sub-groups. These include *CRLF2* overexpression, *IKZF* deletions, *ABL*-class genes uniting, *JAK2* or *EPOR* rearrangements or fusions, *JAK-STAT*, or *MAPK* pathways activation, and other rare variations.

CRLF2 *Displacement.* The *CRLF2* gene is spotted at chromosome XP22.3/YP111.3, which encodes the cytokine receptor-like factor 2 (thymic stromal lymphopoietin receptor). Rearrangement of *CRLF2* accounts for 42% to 60% of Ph-like ALL in the 10- to 39-year age group.[8] It was reported that, along with mutation of the *JAK* family, *CRLF2* overexpression was constitutively present. However, *CRLF2* overexpression is more commonly associated with *JAK2* when compared with *JAK1* and *JAK3*.[14,23] Elevated *CRLF2* expression also results from cryptic deletion and translocation with the *P2RY8-CRLF2* in young children and *IGH-CRLF2* in young adults.[19] Overexpression of *CRLF2* in B-ALL is also stimulated by gain-of-function mutations, which could either be *CRLF2* itself or its partner gene, *IL7RA*.[19]

IKZF *Deletions. IKAROS* zinc finger family transcription factors is a protein encoded by the *IKZF* gene. It plays a very important role in the development and maturation of lymphoid progenitors.[24,25] *IKZF* deletions with certain non-coding single nucleotide polymorphism makes it prone to develop B-lineage ALL.[26] This deletion is common in B-ALL with or without the *BCR-ABL* translocation.[11,27] It is seen in 15% to 30% in *BCR-ABL*-negative ALL and 60% in *BCR-ABL*-positive ALL.[28,29] The deletion is also established as a poor prognostic factor in both high-risk and standard-risk patients in all age groups.[30,31] In terms of pathogenic events, it disturbs normal B cell differentiation and triggers uncontrolled leukemic cell proliferation. It has a unique adhesive property that aggravates the cell division. The adhesive power of *IKZF* leads to leukemogenesis and aberrant adhesion of leukemic cells to bone marrow recess. These leukemic cells provide resistance to TKIs, which may be counteracted by retinoic acid compounds and *FAK* inhibitors. Owing to this mechanism, Ph-like ALL shows inferior outcomes and poorer prognosis.[11,32,33]

ABL *Class Rearrangements.* One of the most important subtypes, accounting for 10% of Ph-like ALL. It occurs in 17% of children, 9% of adolescents, 10% of young adults, and 9% of older adults.[7,8,10] *ABL* class activates the signaling pathways that mediate the pathophysiology of Ph-like ALL. This group includes kinases *ABL1*, *ABL2*, *PDGFRA*, *CSF1R*, *PDGFRB*, and *LYN*.[4] Patients with translocations, particularly *PDGFRB*, have shown induction failure. As an adjunct to conventional chemotherapy, TKI inhibitors

Table 2 Treatment Outcome of Ph-like ALL

A. Treatment Outcome of Ph-like ALL in Pediatric Patients

Clinical Trial	Age, y	Risk Group	Ph-like ALL Number and Prevalence %		Treatment Outcome	
			No.	%		
P9906 Mullighan et al[11]	1-18	High-risk	31	68	5-y EFS	25.9% ± 10%
COALL 92/97 Den Boer et al[2]	0-18	All	19	28	5-y DFS	59.5%
DCOG-ALL-8/9 Den Boer et al[2]	0-18	All	15	10	5-y DFS	57.1%
AALL0232 Loh et al[9]	1-18	High-risk	14	81	5-y EFS	62.6% ± 6.9%
DCOG-ALL-8/9/10 Vander Veer et al[12]	1-18	All	16	94	5-y CIR	32%
Multiple trials	1-15	Standard-risk	10	33	—	—
Roberts et al[8]	1-15	High-risk	12.7	108	5-y EFS	58.2% ± 5.3%
Roberts et al[8]	16-20	All	20.6	77	5-y EFS	41.0% ± 7.4%
St. Jude Total XV Roberts et al[3]	1-18	All	11.6	40	5-y EFS	90.0% ± 4.7%

B. Treatment Outcome of Ph-like ALL in Adolescents and Young Adults

Clinical Trial	Age, y	Risk Group	Ph-like ALL No. and Prevalence %		Treatment Outcome	
			No.	%		
Roberts et al[8]	21-39	All	27.4	46	5-y EFS	24.1% ± 10.5%
University of Pennsylvania Tasian et al[14]	18-39	All	25.9	7	—	—
Multiple trials Roberts et al[3]	21-39	All	27.9	96	5-y EFS	24.1%

C. Treatment Outcome of Ph-like ALL in Older Adults

Clinical Trial	Age, y	Risk Group	Ph-like ALL No. and Prevalence %		Treatment Outcome	
			No.	%		
Roberts et al[8]	21-39	All	27.4	46	5-y EFS	24.1% ± 10.5%
University of Pennsylvania Tasian et al[14]	18-39	All	25.9	7	—	—
Multiple trials Roberts et al[3]	21-39	All	27.9	96	5-y EFS	24.1%

Abbreviations: CIR = cancer immune responsiveness; DFS = disease-free survival; EFS = event-free survival; Ph-like ALL = Philadelphia-like acute lymphoblastic leukemia.

such as imatinib and dasatinib are commonly used in order to down-regulate the manifestations of translocations.[8]

JAK2-STAT *Signaling*/EPOR *Rearrangements.* One-half of the patients of Ph-like ALL with *CRLF2* rearrangement have concomitant activating mutation of Janus Kinase gene, *JAK1* and *JAK2*, which leads to the activation of the *JAK-STAT* signaling pathway.[14,30,31] The frequency of *JAK* mutations in adults with *CRLF2* rearrangement is lower with *JAK* wild-type, which is 1:4.[7] There are several other gene-based phenomena that cause *JAK-STAT* signal activations. It can be *JAK* mutations with or without *JAK2* fusions, EPOR rearrangement encoding the erythropoietin receptor, and rarely involves *IL7R, SH2B3,* and others.[7,8,10] The independent rearrangements of *JAK2* and *EPOR* occur in approximately 7% and 5% cases of Ph-like ALL, respectively. Thus far, 20 different *JAK2* fusions have been recognized, which makes it the most heterogeneous gene in Ph-like ALL. Four different types of *EPOR* rearrangements have been identified. *JAK* inhibitors like ruxolitinib can be a productive therapy that targets the *EPOR/JAK* rearrangements and other activating mutations.[15,18,34]

A few rare kinase driven mutations are also found in the genomic profile of Ph-like ALL, which involves *BLNK, NTRK3, TYK2, PTK2B, FGFR1,* etc. *FLT3* mutation is most common in high-risk ALL.[7,8,10] *ETV6-NTRK3* (tropomyosin receptor kinase), a rare but repeated mutation, was defined in 1% of Ph-like ALL.[35] However, the oncogenic role of *ETV6-NTRK3* in B-ALL is not yet established. It has been identified in only 1 study, conducted in the conditional knock-in mouse model, that the activation of *ETV6-NTRK3* using CD19-Cre could result in the rapid development of pre-B ALL with complete penetrance and infiltration of leukemic blasts into multiple organs, including bone marrow, spleen, and the central nervous system.[35] An efficient treatment with the *TRK* inhibitor larotrectinib decreases the burden to some extent.[36]

In addition, there are other genes such as *KRAS, NRAS, NF1, PTPN11,* etc., which can cause mutations in the RAS pathway. Such deficiency is found in 4% of patients with Ph-like ALL. Deviations in this pathway are frequently seen with *MLL* rearrangement. *MEK* inhibitors are considered as a novel therapeutic route for Ph-like ALL with *RAS* mutations.[7,8,10] *ETV6-NTRK3* fusion is one of the indications of an activated RAS pathway. The fusion has been diagnosed in various types of malignancies, such as secretory breast carcinoma, congenital fibrosarcoma, and pediatric pontine glioma. TRK inhibitors such as

Table 3 Kinase Alterations in Ph-like ALL

Class	Incidence[13]	Kinase Gene	Number of Fusion Partners	Fusion Partner Genes	Potential TKI
ABL	Children, 16.7% Adolescents (16-21 y), 9% Young adults (21-39 y), 10.4% Adults (40-86 y), 9.2%	*ABL1*	12	*CENPC, ETV6, FOXP1, LSM14, NUP214, NUP153, RCSD1, ANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1*	Dasatinib
		ABL2	3	*PAG1, RCSD1, ZC3HAV1*	Dasatinib
		CSF1R	3	*MEF2D, SSBP2, TBL1XR1*	Dasatinib
		LYN	2	*NCOR1, GATAD2A*	Dasatinib
		PDGFRA	1	*FIP1L1*	Dasatinib
		PDGFRB	7	*ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8*	Dasatinib
JAK-STAT	Children, 24.1% Adolescents (16-21 y), 32% Young adults (21-39 y), 14.6% Adults (40-86 y), 11.2%	*CRLF2*	2	*IGH, P2RY8*	*JAK* inhibitor *PI3K/mTOR* inhibitor
		JAK2	20	*ATF7IP, BCR, EBF1, ETV6, GOLGA5, HMBOX1, OFD1, PAX5, PCM1, PPFIBP1, RFX3, SMU1, SNX29, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274, ZBTB46,*	*JAK* inhibitor *PI3K/mTOR* inhibitor
		EPOR	4	*IGH, IGK, LAIR1, THADA*	*JAK* inhibitor
		TYK2	3	*MYB, SMARCA4, ZNF340*	*TYK2* inhibitor
		IL2RB	1	MYH9	*JAK* inhibitor
		JAK1	0	N/A	*JAK* inhibitor
		JAK3	0	N/A	*JAK* inhibitor
		IL7R	0	N/A	*JAK* inhibitor
		SH2B3	0	N/A	*JAK* inhibitor
Others	Children, 2.8% Adolescents (16-21 y), 3% Young adults (21-39 y), 5.2% Adults (40-86 y), 3.1%	*NTRK3*	1	*ETV6*	*TRK* inhibitor
		FLT3	1	*ZMYM2*	*FLT3* inhibitor
		FGFR1	1	*BCR*	*FGFR* inhibitor
		BLNK	1	*DNTT*	Unknown

Abbreviations: Ph-like ALL = Philadelphia-like acute lymphoblastic leukemia; TKI = tyrosine kinase inhibitor.

larotrectinib and ALK inhibitors like crizotinib are currently being used as target therapy.[37]

Incidence

As reported in Table 1, the incidence of Ph-like ALL varies with age in different studies. In adolescents and young adults, it ranges from 18% to 42%,[4-10] in children, it is 13%,[8] and in older individuals, it ranges from 7% to 25%.[4-7]

The highest incidence was reported by GEP in the 15- to 39-year-old age group. Other techniques like flow cytometry, fluorescence in situ hybridization, and sequencing have reported an uneven range from 18% to 27%.[4,5] A study using new techniques, such as Affymetrix U133 Plus Version 2.0 gene expression microarray, Affymetrix SNP Version 6.0 microarray profiling, and Sanger sequencing using prediction analysis of microarray, reported Ph-like ALL in 14% of the patients.[9]

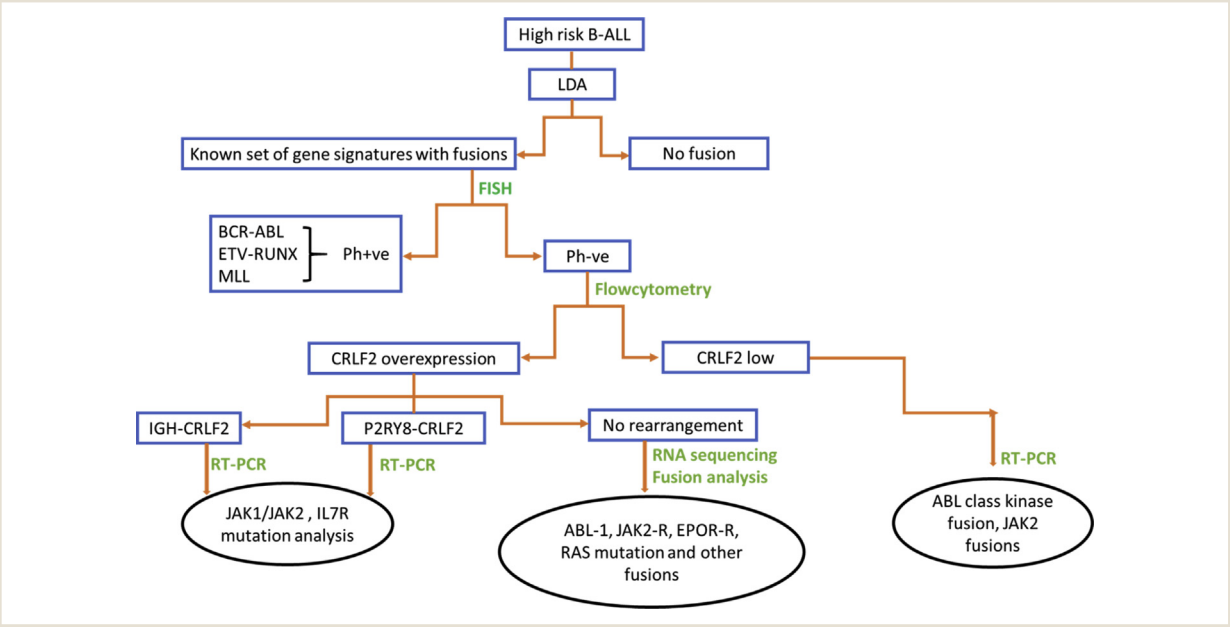
The incidence may vary depending upon the type of tests that is used to detect or define Ph-like ALL. Most of the multi-centric studies applied gene expression profiling using either U133 Plus 2.0 microarrays or low-density arrays (LDAs) as a diagnostic tool for Ph-like ALL and reported a high incidence.[4,8,9]

Diagnosis of Ph-like ALL

As seen in Table 1, different studies have used an array of techniques for defining Ph-like ALL. In the updated World Health Organization 2016 classification, *BCR-ABL* like B-lymphoblastic leukemia/lymphoma is defined as "a neoplasm of lymphoblasts committed to the B-cell lineage that lack the *BCR-ABL1* translocations but showing a pattern of gene expression very similar to that seen in ALL with *BCR-ABL1*."

However, the current clinical definition has tried to identify this entity using tools like fluorescence in situ hybridization (FISH), flow cytometry (FCM), and polymerase chain reaction (PCR), as these are more applicable in practice. Using these techniques, different algorithms have been developed to try and define Ph-like ALL.[14] Techniques like GEP/next-generation sequencing (NGS) may not be routinely available for clinical use in many settings. As FCM is routinely available, as well as being a quick, low-cost, and reliable technique, it has been commonly used to detect CRLF2 overexpression in the diagnostic panel. The higher expression of CRLF2 is more commonly associated with its rearrangement in Ph-negative adult patients. Metaphase FISH was also performed to identify rearrangements, including CRLF2-IGH and CRLF2-

Figure 2 Current Ph-like ALL Genetic Testing Algorithm



Abbreviations: B-ALL = B cell acute lymphoblastic leukemia; FISH = fluorescence in situ hybridization; LDA = low-density array; Ph-like ALL = Philadelphia-like acute lymphoblastic leukemia; Ph-ve = Philadelphia-negative; Ph+ve = Philadelphia positive; RT-PCR = real-time polymerase chain reaction.

P2RY8, and it had shown 100% concordance with the results of multiparameter flow cytometry.[19]

It has been reported in previous studies that *CRLF2* overexpression and rearrangement are commonly accompanied by *JAK1/JAK2* mutation and *IKZF1* deletions.[14] Real-time quantitative PCR (RT-PCR) was performed to assess *CRLF2* overexpression.[23] *P2RY8-CRLF2* transcript was identified by RT-PCR. *JAK* mutation was examined by PCR amplification and Sanger sequencing. *IKZF1* deletion was detected by Multiplex ligation-dependent probe amplification.[23]

With respect to the identification of cryptic translocations and MRD-sensitive markers, the RT-PCR technique has emerged as a gold standard diagnostic tool over conventional cytogenetics.[38] The RT-PCR assay was developed to detect specific gene fusions by using a panel of individual monoplex assays. The tedious procedure of detecting leukemia gene profiles using individual monoplex assays has been eased out following the utility of multiplex RT-PCR, especially when we need to evaluate multiple leukemia translocations in the same specimen.[39]

In a few clinical trials, the researchers performed quantitative RT-PCR–based LDA to assess CRLF2 expression and rearrangements and subsequently for kinase alterations. To confirm CRLF2 rearrangement and other *JAK1*, *JAK2,* and *IL7R* mutations, the Sanger sequencing technique was also used. This way of investigation is tiring and cumbersome but advantageous for a large number of patients in multi-centric studies.[19]

DNA- and RNA-based sequencing, such as whole genome, whole exome, and whole-transcriptome sequencing, are the most comprehensive techniques to examine single nucleotide variants and structural and copy number variation, which provides adequate information about Ph-like ALL.

Prognostic Impact

Several kinds of treatment protocols are available for different age groups for Ph-like ALL. As seen in Table 2, it has been observed in previous studies that the survival outcome in children was in the range from 15% to 94%. The highest survival in pediatric ALL, per the St Jude study, is 90%, and yet it is lower compared with Ph-like ALL. In other age groups (ie, adolescents, young adults, and older adults), survival outcomes ranged from 13.6% to 34.6%.[3,8,14] This difference arises despite adopting similar treatment strategies in a few studies.

Similar to age, there are various prognostic factors such as gender, ethnicity, white blood cell count at diagnosis (of greater than 30,000/L [B-ALL]), central nervous system involvement, morphologic, immunophenotype, MRD status, and genetic abnormalities responsible for adverse clinical profiles and inferior outcomes. It has been reported that elevated MRD levels are frequently associated in all the age groups with the high-risk B-ALL subtype.[10,40] These factors play a crucial role in risk stratification. Such risk stratification and exact evaluation of prognosis is a focal point of treatment management.[22]

The prognostic impact of MRD was also observed in the study conducted at the St Jude research center. A risk-directed strategy was followed to measure MRD levels during remission induction therapy. There was no significant difference reported in inferior event-free survival between Ph-like and other subtypes of B-ALL. However, a significantly higher level of MRD was more likely detected in Ph-like ALL, classified as a high-risk group, and this

Table 4 Baseline Characteristics of Included Studies

No	References	ALL, n	Ph-Like ALL, n	Gender (M/F)	Median Age, y (Range)	Median WBC Count × 10^9/L	Ph-like Screening Method Used	Specific Gene Detection Method	Study Period	Study Type
1	Den Boer et al 2009[2]	246	44	NR	6.5	36.5	HC	RT-PCR for kinase method	1990-2004	Prospective
2	Harvey et al 2010[14]	207	29	M, 21 F, 8	14.2	92.7	PAM	FISH, Flow cytometry, PCR	2000-2003	Retrospective
3	Roberts et al 2012[15]	1157	158	NR	NR	NR	PAM	mRNA sequencing, WGS, RT-PCR, SNP array analysis	2000-2010	Retrospective
4	Maude et al 2012[16]	21	18	NR	NR	NR	Xenograft models	Phosphoflow cytometry, immunoblotting	NR	Retrospective
5	Loh et al 2013[9]	572	81	NR	NR	NR	PAM	FISH, RT-PCR	2000-2010	Retrospective
6	Veer et al 2013[12]	1128	94	NR	NR	NR	HC	Multiplex ligation-dependent probe amplification	1994-2015	Retrospective
7	Roberts et al 2014[3]	344	40	M, 27 F, 13	5.3 (1.3-18.6)	7.1 (1.7-258.3)	PAM	FISH, RT-PCR, RNA sequencing, Sanger sequencing (NGS), genomic PCR	2000-2007	Prospective
8	Roberts et al 2014[8]	1725	264	NR	NR	NR	PAM	FISH, RT-PCR, RNA sequencing, genome sequencing (NGS)	2000-2007	Retrospective
9	Boer et al 2015[6]	127	21	NR	25 (16-59)	NR	HC	RT-PCR	1993-2009	Prospective
10	Andreu et al 2015[17]	308	44	NR	NR	NR	PAM	NR	NR	Retrospective
11	Jain et al 2016[4]	148	49	NR	NR	NR	PAM	Flow cytometry, FISH	NR	Retrospective
12	Iacobucci et al 2016[18]	3115	212	NR	NR	NR	NR	Sanger sequencing, whole genome sequencing	NR	Retrospective
13	Konoplev et al 2017[19]	126	10	NR	NR	NR	Multiparameter flow cytometry	Multiparameter flow cytometry, FISH	2013-2015	Prospective
14	Tasian et al 2017[20]	87	18	NR	28.6 (19-63)	28.6	PAM	FISH, RT-PCR	NR	Retrospective
15	Herold et al 2017[5]	207 (B-ALL)	26	NR	31 (16-69)	NR	PAM	FISH, RT-PCR, Copy number alterations were analyzed using the SALSA multiplex ligation-dependent probe amplification kit P335-B1	1999-2005	Retrospective
16	Heatley SL et al 2017[21]	245	19	NR	NR	NR	PAM	FISH, NGS, SNP Microarray	2002-2011	Retrospective
17	Roberts et al 2017[7]	798	194	M, 119 F, 73	40 (21-86)	56.6 (0.2-434) (range)	PAM	FISH DNA copy number alterations SNP profiling	NR	Retrospective
18	Reshmi et al 2017[10]	1389	284	NR	NR	NR	TaqMan LDA PCR assay	Reverse transcriptase PCR, Transcriptome sequencing, FISH	2010-2014	Retrospective
19	Roberts et al 2018[22]	1023	139	NR	<10 years	<50	8-gene TaqMan LDA PCR assay	TaqMan PCR on the LDA card, FISH, Sanger sequencing, RT-PCR, Transcriptome sequencing analysis	2006-2008	Retrospective

Abbreviations: F = female; FISH = fluorescence in situ hybridization; HC = hierarchical clustering; LDA = low-density array; M = male; NGS = next-generation sequencing; NR = not reported; PAM = prediction analysis for microarrays; PCR = polymerase chain reaction; Ph-like ALL = Philadelphia-like acute lymphoblastic leukemia; RT = real-time; SNP = single nucleotide polymorphism; WBC = white blood cell; WGS = whole genome sequencing.

group received hematologic stem cell transplantation (HSCT) for further treatment.[3]

Treatment Targets

As discussed in previous sections, conventional chemotherapy produces poor outcomes in Ph-like ALL. Hence, there is a need for developing newer approaches. Although there is extensive genetic heterogeneity, *ABL* and *JAK-STAT* mutations are the most commonly involved genes that can be targeted for therapy (Table 3). This table shows various treatment targets in Ph-like ALL.

ABL Targeted Pathway

Patients presenting ABL class rearrangements are around 10% to 15% (17% of children, 9% of adolescents, 10% of young adults, and 9% of older adults) of patients with Ph-like ALL.[7,8,10] There are approximately 12 gene fusions in this cohort that are targeted with the ABL1 inhibitor, imatinib, and the dual ABL1/SRC inhibitor, dasatinib, by inhibiting the downstream signaling induced by each of these chimeric fusion proteins both in-vitro and in-vivo.[8,15,34] Remarkable results were observed with the particular group *PDGFRB*, which is known for its adverse outcome.[40-43] In the AALL1131 clinical trial, the Children's Oncology Group is investigating the competence of dasatinib in newly identified National Cancer Institute-defined high-risk patients. Accustomed augmented Berlin-Frankfurt-Münster-based chemotherapy is combined with dasatinib from the start of consolidation to maintenance therapy.[44]

JAK-STAT *Signaling Targeted Pathway*

The result of activation of the *JAK-STAT* signaling pathway coincides with the number of gene aberrations with or without *JAK-STAT* mutation, *CRLF2*, *EPOR* and other minor *IL7R*, *SH2B3* rearrangements.[45] Among these, the JAK1/JAK2 inhibitor, ruxolitinib, has been identified as most effective against JAK-STAT—activating alterations (JAK1, JAK2, JAK3, IL7R, IL2RB), but not TYK2).[34] In combination with dexamethasone, type 2 *JAK* inhibitors also provide an adequate response. Based on their functional mechanism, type 2 *JAK* inhibitors are found to serve as a potent target strategy for those with *CRLF2* rearrangements.[46,47]

Although *ABL1*-class and *JAK-STAT* alterations account for the majority of Ph-like ALL cases targeted by TKI inhibitors, there are several other alterations involving kinases that are neither inhibited by ABL class nor *JAK* inhibitors (eg, *BLNK*, *NTRK3*, and *TYK2*).[34] It was observed that the activation of these kinases also contributes to B-ALL disease progression. There are various *TRK* targeting inhibitors, such as entrectinib and larotrectinib, which provide impressive and robust impact in-vitro and in-vivo treatment.[35] A 75% overall response of 55 patients was reported in 3 studies that were conducted using larotrectinib.[47]

At the end of induction and during the early consolidation period, the finding of higher MRD levels emphasizes an inferior outcome in Ph-like ALL. Other than several treatment strategies depending upon specifically targeted molecules, immunotherapy has recently gained significance. This treatment option has a combination of monoclonal antibodies including blinatumomab, inotuzumab, and chimeric antigen receptor (CAR)-T cells, which offers a promising alternative approach wherein CD19-positive cells by blinatumomab, CD22-positive cells by inotuzumab, and both the positive CD cells are lysed by CAR-T cells, which stimulate the immune system after binding in B-ALL cases.[48,49]

As reported in previous studies, chemotherapy followed by allogeneic HSCT (alloHSCT) has improved the survival outcome in B-ALL with BCR-ABL translocations and patients who are MRD-positive.[48,50] However, for BCR-ABL-like ALL, the data to demonstrate the effect of alloHSCT in outcomes is still not available.

Conclusion

The evidence and results obtained from preclinical studies would play a great role in the future treatment approach for Ph-like ALL. The success of combinatorial treatment of *TKI* with chemotherapy in the setting of Ph-positive ALL suggests that this approach may similarly improve outcomes in patients diagnosed with Ph-like ALL. To date, no ideal therapy has been defined for relapse-free survival. Although various research studies and trials are still under process to find therapeutic strategies for these patients, there is potential for further research and clinical trials that would enable us to understand the complexity of the disease. There is also a need to formulate an approach for identifying the genetic modifications responsible for the disease and diagnostic approaches at the earliest.

Disclosure

The authors have stated that they have no conflicts of interest.

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