How is the Ph-like signature being incorporated into ALL therapy?

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Abstract

Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) is a recently identified high risk disease subtype characterized by a gene expression profile similar to that observed in Philadelphia chromosome-positive (Ph-positive) ALL, but without an underlying *BCR-ABL1* translocation. Adults and children with Ph-like ALL harbor a diversity of alterations that all lead to activated kinase signaling. Outcomes for patients with Ph-like ALL are poor, which has prompted investigation into the role of tyrosine kinase inhibitor (TKI)-based therapies for this disease. Several clinical trials are now ongoing that include screening for the Ph-like signature and treatment of patients with Ph-like ALL with TKI therapy. This review examines how testing for Ph-like ALL is being incorporated into clinical trials.

Keywords

1. Introduction

Leukemia was introduced into the medical lexicon in the mid-1840s by Rudolf Virchow, but the earliest descriptions of the disease date back to the early 1800s [1]. These earliest reports consist of physical descriptions of patients with particular focus on the gross and microscopic appearance of their blood [2–4]. Over the past centuries, several essential milestones have been achieved in defining unique subsets of leukemia and understanding underlying disease biology. These advances have ranged from phenotypic classification of lymphoid and myeloid leukemias in the early 1900s to the initial descriptions of leukemia cytogenetics in the 1950s and the discovery of the Philadelphia (Ph) chromosome in 1959

[5–8]. In the ensuing decades, continued improvements in acute lymphoblastic leukemia (ALL) survival were attributed largely to successive refinements in risk classification and treatment stratification based on sentinel cytogenetic lesions, early response and other clinical variables.

In recent years, genome-wide profiling studies have led to further refinements in disease classification by defining novel ALL subtypes. Philadelphia chromosome-like (Ph-like) ALL, which has a gene expression profile (GEP) similar to that of Philadelphia chromosome-positive (Ph-positive) disease, but without the presence of the *BCR-ABL1* translocation [9,10], is an example of one of these recently identified poor risk subtypes. In this article, we review the distinctive clinical features of Ph-like ALL and describe how real-time assessment for the Ph-like signature is being incorporated into contemporary ALL treatment protocols.

2. Clinical and biological features of Ph-like ALL

There are approximately 5000 new cases of ALL in the United States every year with over half arising in children and adolescents ages 0–19 years [11]. ALL is the most common cancer diagnosis in this age group with an incidence rate of 4.4 per 100,000 persons [11]. Age at diagnosis has continued to be one of the strongest prognostic factors [12,13]. While children ages 1–9 years have 5-year overall survival (OS) rates of greater than 90%, this number decreases to less than 70% in adolescents ages 15–19 years and continues to decline to approximately 35% in the young adult population ages 25–39 years [14]. The reasons behind these survival differences are multifactorial and include variability in treatment, unique toxicity profiles, complex psychosocial factors, and biological differences in disease [15,16].

Recent genomic discoveries have enabled more precise disease classification and provided insight into why inferior responses to traditional chemotherapeutic regimens may be observed in some disease subtypes. One of these most recent discoveries has been the identification of Ph-like ALL [9,10]. This high risk subtype has a peak prevalence in adolescents and young adults and may account, in part, for their inferior outcomes compared to younger children. In addition to older age at diagnosis, the Ph-like GEP is associated with other adverse clinical features. Several studies have established that children and adults with Ph-like ALL have higher white blood cell (WBC) counts at presentation [10,17,18]. Additionally, patients with Ph-like ALL have high rates of minimal residual disease (MRD) at the end of induction [17,19–21]. Ph-like ALL is also more common in patients of Hispanic and Native American ethnicity [20,22]. Notably, the frequency of self-declared Hispanic ethnicity was 37% among 284 children, adolescents, and young adults with Ph-like ALL in a recent study [18].

2.1. Prevalence and outcome

The prevalence of Ph-like ALL varies significantly across the age spectrum (Table 1). Increasing prevalence of Ph-like ALL with age has been reported in one large pediatric and adolescent/young adult (AYA) study, ranging from 10% in younger children (1–10 years) to 28% in young adults (21–39 years) [21,23]. Although there have been conflicting reports

regarding the frequency in the older adult population (age 40 years), recent studies have identified the Ph-like signature in 13–33% of older adults [19,20,23–25]. These variations in the reported prevalence are attributed, in part, to differences in the race and ethnicities of the populations studied and differences in the GEPs used to classify Ph-like disease [20,26].

Ph-like ALL has been consistently associated with decreased OS and event-free survival (EFS) among all age groups [9,10,17,20–24,26–29] (Table 1). One study demonstrated non-inferior outcomes in a cohort of Ph-like ALL patients with risk-directed therapy. This study, however, included younger patients with an allocation to hematopoietic stem cell transplantation for many patients in complete first remission based on initial MRD response [30].

2.2. Genetic characterization

Rearrangements in genes involved in cytokine receptor and kinase signaling are a hallmark of Ph-like ALL, identified in 80–90% of cases. Although the frequency and spectrum of underlying genetic alterations varies among different age groups and populations, most involve activation of ABL and/or JAK-STAT signaling pathways as a common mechanism of transformation. These alterations can be grouped into six categories: 1) *CRLF2* rearrangements with or without *JAK1* or *JAK2* mutations, 2) ABL-class fusions (rearrangements in *ABL1*, *ABL2*, *CSF1R* or *PDGFRB*), 3) *JAK2* or *EPOR* rearrangements, 4) other mutations or alterations involved in JAK-STAT signaling, 5) Ras pathway alterations, and 6) other kinase alterations [21,23] (Fig. 1). As in (Ph-positive) ALL, deletions in the *IKZF1* (*Ikaros*) lymphoid transcription factor have been reported in approximately 70% of children and adults with Ph-like ALL [9,10,23].

Specific genetic alterations have been associated with age at diagnosis. *CRLF2* rearrangements are the most common finding in Ph-like ALL. The frequency of these rearrangements also increases with age, occurring in up 60% of adolescents and adults [20,21]. *CRLF2* rearrangements are accompanied by *JAK1* or *JAK2* mutations in approximately half of all cases [18]. Regardless of *JAK* mutational status, however, *CRLF2*-rearranged leukemias appear susceptible to JAK pathway inhibition in preclinical studies [31,32]. Herold et al. reported that the frequency of *JAK2* mutations and *IGH-CRLF2* rearrangements increase significantly with age 16 years in adults [19], a finding in agreement with a recent report from the MD Anderson Cancer Center (MDACC) [20]. In another recent report of Ph-like ALL in adults, approximately 70% harbored genetic alterations that may be targetable with JAK inhibitors, (e.g., *CRLF2* rearrangements, *JAK2*or *EPOR* rearrangements, and *IL7R* mutations) [23].

ABL-class fusions are the second most common alteration in Ph-like ALL, occurring in approximately 10–15% of children and adults with Ph-like ALL [18,21,23]. *JAK2* and *EPOR* rearrangements and other JAK-STAT signaling pathway alterations are observed most frequently in the young adult population (age 21–39 years) [21,23]. Isolated Ras pathway alterations make up a minority of alterations in all populations [21,23]. Currently, 10–11% of children and adults with Ph-like ALL have unknown alterations [21,23].

While patients with Ph-like ALL experience inferior outcomes compared to those with non-Ph-like B-ALL, specific alterations appear to have different prognostic importance [21,22,29]. Patients with *IKZF1* alterations, regardless of other expression profiles, may have inferior outcomes with a 5-year overall survival (OS) of 20% in young adults [9,10,21,23]. Among children and AYAs (ages 1–39 years), *JAK2* and *EPOR* rearrangements portend poor outcomes with 5 year EFS of 26.1% [21]. In contrast, favorable outcomes with 5-year EFS of 86% were observed in patients with isolated Ras pathway alterations [21]. *CRLF2* overexpression in adults has been associated with significantly worse outcomes with 5-year survival <20% [20].

3. Diagnostic algorithms

Given the prevalence of Ph-like ALL and the poor outcomes that have been observed with conventional therapy, screening algorithms for the Ph-like signature have now been developed to facilitate real-time treatment stratification. Adult and pediatric treating groups have used a number of different approaches ranging from selected screening of patients with high risk clinical features, such as high mid- and end of induction disease burdens [33–35], to the use of more comprehensive gene expression profiling or next-generation sequencing in all newly diagnosed patients. While the strategies used to define the Ph-like signature vary [26], the overall goal of diagnostic testing is accurate identification of the underlying genetic alterations such that treatment can be modified accordingly.

3.1. Tiered approaches

The Children's Oncology Group (COG) is now screening all National Cancer Institute (NCI) high risk (HR) patients with newly diagnosed B-ALL for the Ph-like GEP with a quantitative reverse transcriptase polymerase chain reaction (RT-PCR)-based low density array (LDA) platform [18]. The GEP of Ph-like ALL was used to design an LDA card where the expression of 8 or 15 genes is highly predictive of the Ph-like ALL signature. Patients with an LDA coefficient of 0.5–1 are designated positive for Ph-like ALL [18]. A series of downstream tests are performed in dedicated reference laboratories in those patients who are LDA screen positive. *CRLF2* is among the genes assessed in the LDA classifier, which can also directly assess for the presence of *P2RY8-CRLF2* fusion. In *CRLF2*-overexpressing cases without this fusion, fluorescence *in situ* hybridization (FISH) is then performed to identify *IGH-CRLF2* rearrangements. *JAK1* and *JAK2* mutation testing is next completed in all patients with confirmed *CRLF2* rearrangements. In Ph-like cases without *CRLF2* rearrangements, RT-PCR assays are done to detect ABL class, JAK2, and other known kinase fusions with confirmation by Sanger sequencing. Finally, RNA sequencing or alternate testing is performed on remaining LDA-positive cases without otherwise defined genetic alterations. This testing for Ph-like ALL is now being performed in real-time for patients with HR B-ALL enrolled on the COG AALL1131 phase 3 clinical trial (NCT02883029) within the first 4 weeks of therapy so that patients with confirmed targetable mutations or fusions can be allocated to TKI-containing treatment after completion of induction therapy (Fig. 2). Other groups have adopted a similar approach. While tiered screening and testing approaches have practical advantages in clinical trials that accrue large numbers of patients, some alterations can be missed, especially as a number of

new fusions and novel breakpoints continue to be discovered [18]. Further, timely completion of all necessary testing by the end of induction can be challenging in some cases with this staged approach.

3.2. Alternative approaches

Recent advances in next-generation sequencing technologies have led to development of DNA- and RNA-based assays capable of highly sensitive detection of leukemia-associated genetic mutations and fusions. In addition to the above RT-PCR assays currently used by the COG reference laboratories [18], several commercially-available platforms (*e.g.*, ArcherDx FusionPlex, NanoString Vantage, FoundationOne Heme, others) can also be used to identify Ph-like ALL-associated alterations. One advantage of these newer technologies is their potential ability to identify fusions involving previously-unknown 5′ partners, as there are a relatively small number of known 3′ partners in Ph-like ALL [18,21]. Finally, unbiased RNA sequencing (RNA-seq; whole transcriptome sequencing) is likely the most comprehensive method for identifying Ph-like ALL fusions, including those unable to be detected by other assays. However, RNA-seq is not widely available at this time as a clinical test and remains relatively costly and labor-intensive with respect to bioinformatic analysis.

4. Treatment of Ph-like ALL

Adult and childhood cancer cooperative groups are now actively developing clinical trials to test the efficacy of addition of kinase inhibitors ruxolitinib or dasatinib to chemotherapy for patients with Ph-like ALL harboring JAK pathway alterations or ABL class fusions, respectively (Table 2).

4.1. JAK pathway alterations

Preclinical studies to date have demonstrated constitutive activation of kinase signaling networks in subsets of Ph-like ALL harboring JAK pathway alterations (described in detail in Chapter 4) [21,31,36,37]. These alterations are the most common finding in Ph-like ALL across the age spectrum. Additional studies have reported activity of various JAK inhibitors in patient-derived xenograft (PDX) models of *JAK* pathway-mutant Ph-like ALL, providing rationale for testing of JAK inhibitor-based therapies in the clinic [32,37–41]. To date, many preclinical studies in ALL models have sought to elucidate anti-leukemia effects of the JAK1/JAK2 inhibitor ruxolitinib, which is approved by the Food and Drug Administration for treatment of patients with *JAK2*-mutant myeloproliferative neoplasms [41–43]. As an initial investigation, the first-in-child phase 1 COG trial ADVL1011 recently demonstrated the safety of ruxolitinib monotherapy in children with relapsed or refractory cancers without a maximum tolerated dose of ruxolitinib identified [44].

The COG is now investigating the potential efficacy of combining ruxolitinib with augmented Berlin-Frankfurt-Münster (BFM)-based post-induction chemotherapy (consolidation through maintenance) in children, adolescents, and young adults with newly-diagnosed HR JAK pathway-mutant Ph-like ALL via the phase 2 trial AALL1521 (NCT02723994). Patients with relevant mutations are identified during induction therapy via the same LDA and molecular analyses as for patients with ABL class-mutant Ph-like ALL

treated with dasatinib on COG AALL1131 (Fig. 2). In AALL1521, patients are stratified by genetic alterations (e.g., *CRLF2* rearrangements versus *JAK2* or *EPOR* fusions) and by end-induction MRD status to elucidate potential differential efficacy of combination therapy in each subset. An embedded dose-finding part of this trial will establish safe and tolerable dosing of ruxolitinib with augmented BFM-based chemotherapy prior to efficacy analyses at the recommended phase 2 dose in larger statistically-powered cohorts of patients. The primary endpoint of this non-randomized phase 2 trial is 3 year EFS versus survival of historic control patients treated with an identical chemotherapy backbone without ruxolitinib [45].

A stratum of the Total XVII trial at St. Jude Children's Research Hospital will also assess the safety of ruxolitinib addition to chemotherapy in children with JAK-mutant Ph-like ALL (NCT03117751). A phase 2 trial of ruxolitinib in combination with multi-agent chemotherapy [hyper-CVAD, high-dose methotrexate and cytarabine, POMP maintenance] in children 10 years and adults with relapsed/refractory JAK-mutant ALL is also ongoing at MDACC (NCT02420717) [46]. In this study, patients with JAK pathway-mutant Ph-like ALL are initially treated with up to three weeks of ruxolitinib monotherapy with subsequent addition of multi-agent chemotherapy for those patients with suboptimal response to single-agent ruxolitinib. The primary outcome measurement is complete response rate after six weeks of reinduction therapy. A separate arm of this trial is similarly assessing the efficacy of dasatinib with chemotherapy in patients with Ph-like ALL harboring ABL class alterations.

4.2. ABL class rearrangements

The second most common subgroup of Ph-like ALL is defined by ABL-class rearrangements involving *ABL1*, *ABL2*, *CSF1R* and *PDGFRB*. Cell lines and human cells expressing these gene fusions, as well as patient-derived xenograft models have demonstrated marked sensitivity to the ABL inhibitors imatinib and dasatinib [21,47]. Following the successful paradigm of combining a TKI with chemotherapy for the treatment of Ph+ ALL in children [48–50], anecdotal reports of favorable responses to TKI therapy in patients of Ph-like ALL have also been described [21,30,51,52].

Several groups are now investigating the addition of dasatinib to conventional augmented BFM-based or hyper-CVAD treatment platforms to determine if this will improve outcomes in patients with Ph-like ALL and ABL class fusions. In the current COG AALL1131 trial, patients with confirmed ABL class fusions begin dasatinib daily in combination with chemotherapy at the start of the consolidation phase and continue until the end of maintenance therapy. The EFS rates of children and AYA treated with dasatinib in combination with chemotherapy will be compared to a historical group from the same protocol treated with chemotherapy alone, before uniform screening for the Ph-like signature was implemented. Similar studies investigating dasatinib in combination with chemotherapy for children with ABL class fusions are underway at St. Jude Children's Research Hospital and the MDACC (Table 2). Given the relative overall rarity of Ph-like ALL, randomized studies to assess the potential benefit of TKI addition will likely require broader collaborations. While a number of questions remain, including the role for emerging

immunotherapies and hematopoietic stem cell transplantation in Ph-like ALL, as well as the potential for emergence of TKI resistance mutations with prolonged daily exposure, the implementation of real-time screening procedures and precision medicine treatment approaches has been a promising advance.

5. Summary

Ph-like ALL is a recently described high risk subtype of ALL caused by rearrangements and mutations that activate cytokine receptor and tyrosine kinase signaling. Ph-like ALL occurs in up to one quarter of adolescents and adults with B-ALL, warranting efficient diagnostic screening in these patient populations. While a tiered diagnostic approach may be most cost effective and pragmatic in large clinical trials, ongoing discovery of new genetic alterations may warrant broader and unbiased testing such as RNA-seq. Preclinical evidence and anecdotal reports support a precision medicine treatment approach for Ph-like ALL. However, optimal therapy has not yet been defined, and prospective trials evaluating TKIs in combination with chemotherapy are currently underway.

Acknowledgments

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Practice Points

- Ph-like ALL has a gene expression profile similar to Ph-positive ALL, but lacks *BCR-ABL1* and has been independently associated with a poor prognosis.

- Ph-like ALL occurs in up to one quarter of adolescents and adults with B-ALL.

- The majority of patients with Ph-like ALL have underlying genetic alterations in kinase or cytokine receptor signaling pathways targetable with available TKIs.

- Given the prevalence, prognostic significance, and potential treatment implications, testing for Ph-like ALL should be considered in high risk populations.

Research agenda

- There is a need for ongoing investigation to further characterize the underlying genetic alterations in Ph-like ALL.

- High risk patient populations with B-ALL should have access to testing for the Ph-like signature.

- Given the rarity of this disease subtype, research collaborations will help to define the optimal treatment approach for Ph-like ALL.
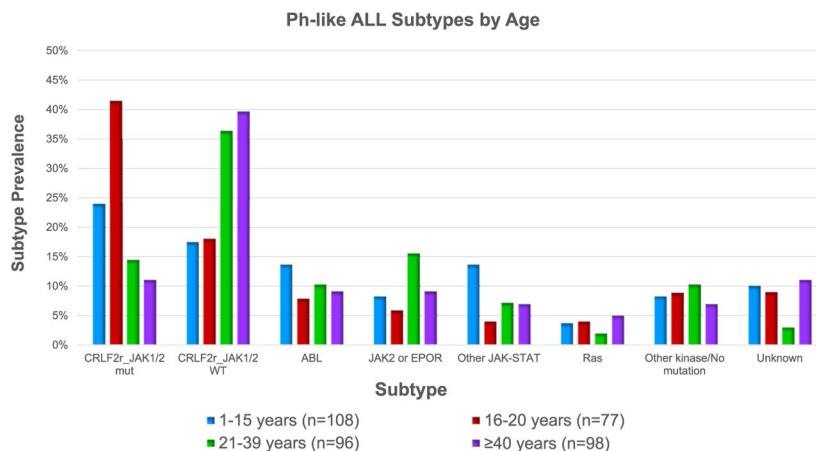
Fig. 1. Ph-like ALL subtypes by age

CRLF2 rearrangements separated by *JAK* status, mutant (mut) or wild-type (WT). ABL-class fusions: *ABL1*, *ABL2*, *CSF1R*, and *PDGFRB*. *JAK2* or *EPOR* rearrangements. Other JAK-STAT: *FLT3* (1–15 years), *IL7R*, *SH2B3*, *JAK1/3*, *TYK2*, *IL2RB* (1–15 years), and *TSLP* (1–15 years). Ras pathway: *KRAS*, *NRAS*, *NF1*, *PTPN11* and *BRAF* (1–15 years). Other kinase/No mutation: Assorted kinase lesions or no kinase-activating alteration identified. Unknown: lacked material for genomic analysis. Data adapted from references 21 and 23.
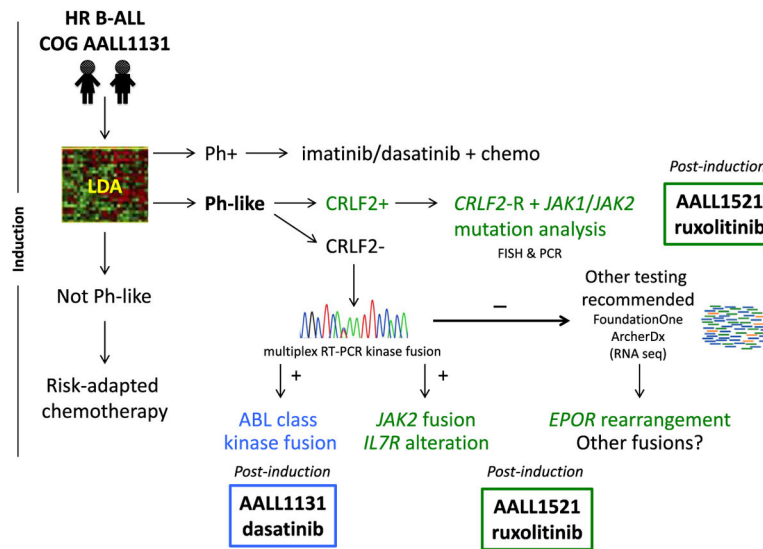
Fig. 2. Diagnostic algorithm for identifying children with Ph-like ALL in real-time
Patients with confirmed ABL class (blue) or JAK pathway (green) alterations are eligible to receive dasatinib (COG AALL1131) or ruxolitinib (COG AALL1521), respectively, in combination with chemotherapy post-induction.

Table 1

Frequency and outcomes of Ph-like ALL in children, adolescents and adults.

Study	Age (years)	Total (Ph-like)	Frequency Ph-like	Outcomes (Ph-like vs. B-other)
Jain et al. [20]	15–39	80 (33)	42%	5-yr OS (all ages) 23% vs. 59% (p = 0.006)
	40–84	68 (16)	24%	
Herold et al. [19]	16–20	26 (5)	19%	5-yr DFS (all ages) 19% vs. 57% (p = 0.001)
	21–39	68 (12)	18%	5-yr OS (all ages) 22% vs. 64% (p = 0.006)
	40–55	45 (4)	9%	
	55–84	67 (5)	7%	
Boer et al. [24]	16–20	24 (6)	25%	5-yr EFS (all ages) 24% vs. 42% (NR)
	21–39	48 (9)	19%	5-yr OS (all ages) 33% vs. 50% (NR)
	40–71	55 (6)	11%	
Roberts et al. [23]	21–39	344 (96)	28%	5-yr EFS 24% vs. 61% (p < 0.0001)
	40–59	304 (62)	20%	5-yr EFS 21% vs. 39% (p = 0.0021)
	60–86	150 (36)	24%	5-yr EFS 8% vs. 33% (p = 0.47)
Roberts et al. [21]	1–15	853 (108)	13%	5-yr EFS 58% vs. 84% (p < 0.001)
	16–20	372 (77)	21%	5-yr EFS 41% vs. 83% (p < 0.001)
	21–39	168 (46)	27%	5-yr EFS 24% vs. 63% (p < 0.001)
Loh et al. [17]	1–31	572 (81)	14%	5-yr EFS 63% vs. 86% (p < 0.0001)
Reshmi et al. [18]	1–31	1389 (284)	20%	NR

Jain B-other: non-*BCR-ABL1*. Herold, Boer, Roberts B-other: *KMT2A*-wild type (WT) and non-*BCR-ABL1*. Loh B-other: non-*BCR-ABL1*. Roberts and Loh limited to NCI high risk patients. Reshmi includes patients eligible for Children's Oncology Group high risk B-ALL study AALL1131. OS = overall survival, 5-yr EFS = event-free survival at 5 years, NR = not reported.

Table 2

Current clinical trials of kinase inhibitor-based therapies for children, adolescents, and adults with Ph-like ALL.

Patient population	Age	Disease status	Inhibitor	Trial
Ph-like with ABL class alterations	10 years	relapse	dasatinib	NCT02420717
Ph-like with ABL class alterations	1–30 years	de novo	dasatinib	NCT01406756
Ph-like with ABL class alterations	1–18 years	de novo	dasatinib	NCT03117751
Ph-like with CRLF2/JAK pathway alterations	10 years	relapse	ruxolitinib	NCT02420717
Ph-like with CRLF2/JAK pathway alterations	1–21 years	de novo	ruxolitinib	NCT02723994
Ph-like with CRLF2/JAK pathway alterations	1–18 years	de novo	ruxolitinib	NCT03117751