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Can Ph-like ALL be effectively targeted?

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ABSTRACT

Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) is a high-risk subset of B-cell ALL with a spectrum of underlying genetic alterations that activate kinase or cytokine receptor signaling. Ph-like ALL occurs at all ages but is most common in adolescents and young adults and is postulated to be a factor in the inferior outcomes in this age group. Ph-like ALL confers a poor prognosis with conventional chemotherapy and the pediatric and adult oncology communities are conducting trials utilizing molecularly targeted approaches. In parallel, the role of immunotherapy is being assessed for this unique and biologically diverse ALL subgroup.

Introduction

Outcomes for children with acute lymphoblastic leukemia (ALL) have steadily improved, with 5-year survival rates now exceeding 90%. But this has not extended to adolescents and young adults whose survival rates on recent Children's Oncology Group trials were 77% and who more frequently have high-risk biologic subtypes of disease [1]. One subtype is Philadelphia chromosome (Ph)-like or *BCR-ABL1*–like ALL, which was independently reported in 2009 by Mullighan and colleagues from the Children's Oncology Group (COG) and St. Jude Children's Research Hospital (SJCRH) and den Boer and colleagues from the Dutch Childhood Oncology Group [2,3]. Ph-like ALL has a gene expression profile similar to Philadelphia chromosome-positive (Ph+) ALL but lacks *BCR-ABL1* and has been independently associated with a poor prognosis. Concomitant *IKZF1* alterations occur in approximately 70% of cases and further negatively impact prognosis [4]. Ph-like ALL is characterized by a diverse array of underlying genetic alterations, including rearrangements, sequence mutations, and copy number alterations that activate kinase or cytokine receptor signaling. The most common genetic alterations are rearrangements of *cytokine receptor-like factor 2* (*CRLF2*) involving either *IGH* or *P2RY8*, frequently with concomitant activating *JAK* mutations. *CRLF2* rearrangements (*CRLF2*-R) occur in approximately 50% of patients with Ph-like ALL overall with a higher frequency in adults [5–8]. *CRLF2*-R, along with *JAK2* fusions, *EPOR* rearrangements, and alterations involving *IL7R, SH2B3, JAK1, JAK3, TYK2,* and *IL2RB* constitutively activate JAK-STAT signaling [9]. Additional recurring alterations in Ph-like ALL include ABL-class fusions (*ABL1*, *ABL2*, *CSF1R*, *LYN, PDGFRA,* and *PDGFRB*) in approximately 10%–15% of patients, as well as mutations and rearrangements in Ras signaling pathways (*NRAS, KRAS, PTPN11*) and other rare fusions (*FLT3, FGFR1, NTRK3, BLNK*) [8,10]. The underlying genetic profile of Ph-like ALL also varies with age (Fig. 1). The frequency of *CRLF2*-R, predominantly *IGH-CRLF2* and *JAK2* mutations, increases with age, whereas the frequency of ABL-class fusions declines in adulthood [9,11]. *EPOR* rearrangements and *JAK2* fusions predominate in adults [6]. Importantly from a therapeutic perspective, despite the

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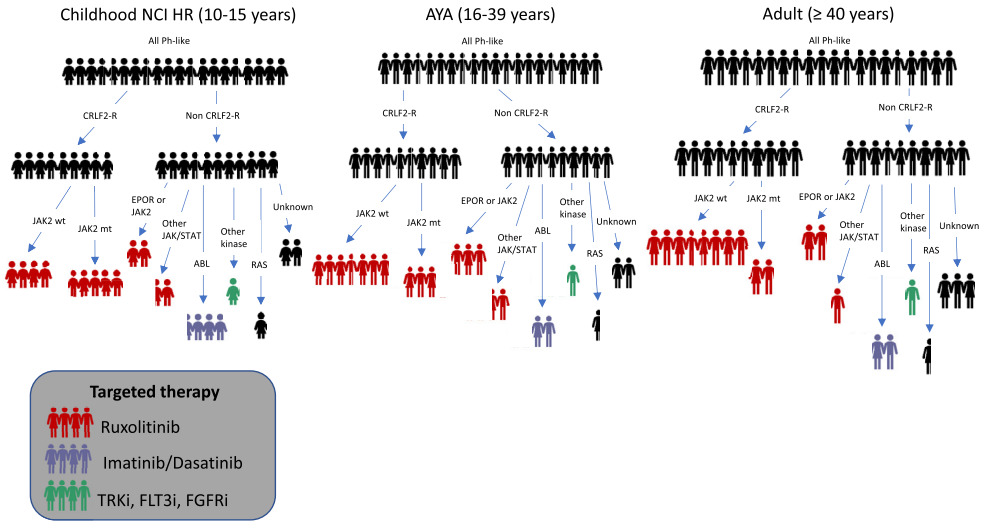

Fig. 1. Prevalence of Ph-like ALL subtypes and available TKI therapy by age.
Other alterations in JAK/STAT: *JAK1/3*, *IL7R*, *SH2BB3*, *TYK2*, and *IL2RB*; ABL-class fusions: *ABL1*, *ABL2*, *CSF1R*, *LYN*, *PDGFRA*, and *PDGFRB*; Ras mutations: *KRAS*, *NRAS*, *NF1*, *PTPN11*, *BRAF*, and *CBL*; other kinase alterations: *FLT3*, *FGFR1*, *NTRK3*. Data adapted from Roberts et al. [5,19].

genetic heterogeneity of Ph-like ALL, the vast majority of cases have alterations that converge on either the ABL or JAK-STAT signaling pathways, which are targetable by available tyrosine kinase inhibitors.

Ph-like ALL prevalence differs according to age with approximate rates of 10% in younger children (1–10 years) and rising to 20%–30% in adolescents and young adults (16–39 years) [5,6]. The reported frequency in older adults ≥40 years ranges widely but averages 20%–24% [6,7,12,13]. This variability is likely attributable to differences in the ethnic backgrounds of the study populations and detection methodologies. Ph-like ALL is more common in males and in individuals with Down syndrome, Hispanic ethnicity, and Native American genetic ancestry [7,9,11,14–16]. It has been associated with high-risk clinical features, including higher presenting white blood cell counts, increased rates of induction failure, and persistent minimal residual disease (MRD) positivity. Accordingly, patients treated with conventional chemotherapy have inferior outcomes [2,5–7,11,13]. Five-year event-free survival (EFS) for Ph-like vs non-Ph-like ALL was 62% vs. 84% ($P < 0.0001$) and 5-year overall survival (OS) was 74% vs 90% on the Children's Oncology Group AALL0232 trial (Fig. 2) [17]. The negative prognostic impact has been even more significant in young adults (21–39 years), where 5-year overall survival for Ph-like ALL was 25% compared to 64% for non–Ph-like ALL ($P < 0.001$) [6]. Given the heightened incidence of the Ph-like signature in adolescents and young adults, this has been postulated to be one of the factors that contributes to inferior outcomes in this population. This also highlights the great potential for precision-based treatment approaches for this high-risk subset.

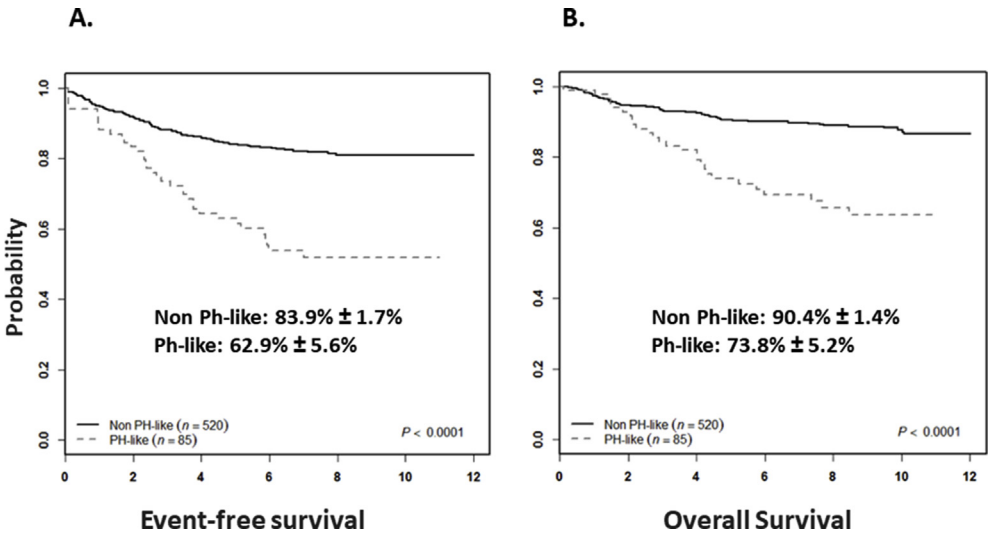

Fig. 2. Outcomes of Ph-like vs Non-Ph-like B-ALL.
Five-year EFS and OS are shown in Ph-like vs non-Ph-like patients. A) EFS; B) OS for high risk B-ALL patients treated on COG AALL0232.

Identifying patients with Ph-like ALL

Given the prognostic implications, it is essential to identify patients with Ph-like ALL in real-time so that novel treatments may be applied. A variety of diagnostic approaches have been developed for identification of the Ph-like genetic signature in B-ALL without a universally accepted standard [16,18,19]. Focused approaches to identify key known fusions among high-risk subgroups offer simplicity and are cost effective. As the Ph-like signature is not found in patients harboring *BCR-ABL1*, *ETV6-RUNX1*, *TCF3-PBX1*, or *KMT2A* translocations, testing can be limited to patient populations without these common cytogenetic findings [20]. Tiered approaches, such as the strategy currently used in several cooperative group trials, employ an initial screening test by either low density array (LDA) expression profile or quantitative real-time polymerase chain reaction (Q-RT-PCR), with more comprehensive downstream testing reserved for those with a positive screening test, thereby limiting more in-depth testing to a minority (10%–30%) of cases [9,18,21]. Comprehensive testing by whole genome, exome, and transcriptome sequencing can identify known as well as novel alterations; however, they are more costly and time consuming at the present time [22]. Various commonly utilized tests are described below.

As flow cytometry is used universally to diagnosis ALL, it is a practical tool to detect the Ph-like signature. *CRLF2* encodes the thymic stromal lymphopoietin receptor (TSLPR), which is over expressed in approximately half of Ph-like B-ALL cases and an ideal candidate for assessment by flow cytometry [23]. Detection of TSLPR/CRLF2 overexpression by flow cytometry has shown to be a reliable and lower cost method for detection of *CRLF2*-R and can be utilized as a readily accessible screening tool for a significant portion of Ph-like B-ALL cases [23–25].

Like flow cytometry, fluorescence in situ hybridization (FISH) studies are performed routinely in the diagnosis and classification of B-ALL and play an important role in characterization of Ph-like disease. There are several commercially available probes targeting genes frequently involved in translocations, including *CRLF2*, *ABL1*, *ABL2*, *PDGFRB, CSF1R,* and *JAK2,* and FISH studies have been incorporated into some Ph-like testing algorithms [9,26]. However, when a rearrangement is detected, further testing is required to determine the translocation partner.

While expansive gene expression profiling (GEP)—the modality used in the original Ph-like description—and next-generation sequencing offer an optimal method for capturing all genetic lesions responsible for Ph-like ALL, these methods are currently labor intensive, time consuming, and costly. Given these limitations, several different screening Q-RT-PCR-based tests have been developed. Harvey and colleagues developed an LDA classifier consisting of an 8- or 15-gene signature with high sensitivity and specificity for identification of Ph-like B-ALL [27]. Several other groups have developed similar Q-RT-PCR-based screening classifiers based on the expression of a limited number of representative genes [28,29]. These screening assays are cost effective and quick turnaround times make them amenable to use in clinical trials that incorporate intervention strategies.

As mentioned, next-generation-sequencing techniques, including whole transcriptome and whole genome sequencing, are the most comprehensive diagnostic tools available. While costly and time intensive, comprehensive sequencing at diagnosis is now performed routinely in children enrolled in clinical trials at SJCRH [22]. Additionally, there are several commercially available platforms, eg, ArcherDX FusionPlex, NanoString Vantage, and FoundationOne Heme that can identify Ph-like genetic alterations within 4 weeks. Given the complexities of Ph-like identification and its implications, utilization of a well-thought-out testing algorithm consisting of a combination of the above techniques maximizes detection and expedites therapeutic interventions.

Therapy for Ph-like ALL

In recent years a number of clinical trials have been developed for children and adults with Ph-like ALL investigating the combination of tyrosine kinases inhibitors (TKIs) with conventional chemotherapy, following the successful paradigm in Ph+ ALL (Table 1) [30,31]. Preclinical studies [32–34] and anecdotal case reports [35–40] have provided support for this treatment approach.

Molecularly targeted approaches

Rearrangements of *CRLF2* and other JAK-STAT pathway alterations targetable with a JAK inhibitor are the most common finding in Ph-like ALL, present in approximately 70% of children and adults with Ph-like ALL [5,6]. Several trials are currently underway investigating the safety and efficacy of ruxolitinib in combination with chemotherapy for JAK pathway altered Ph-like ALL. COG/Incyte AALL1521 is a 2-part phase 2 trial investigating ruxolitinib with post-induction augmented Berlin-Frankfurt-Münster (BFM)-

Table 1
Molecularly targeted therapy for children, adolescents, and adults with Ph-like ALL.

Ph-like alteration	TKI	Disease status	Age	Clinical trial
ABL class	dasatinib	newly diagnosed	1–18 years	NCT03117751
ABL class	dasatinib	newly diagnosed	1–21 years	NCT03020030
ABL class	dasatinib	relapsed	≥10 years	NCT02420717
CRLF2/JAK pathway	ruxolitinib	newly diagnosed	1–21 years	NCT02723994
CRLF2/JAK pathway	ruxolitinib	newly diagnosed	18–39 years	NCT03571321
CRLF2/JAK pathway	ruxolitinib	newly diagnosed	1–18 years	NCT03117751
CRLF2/JAK pathway	ruxolitinib	relapsed	≥10 years	NCT02420717

based chemotherapy for patients 1–21 years of age with newly diagnosed Ph-like ALL with a *CRLF2* rearrangement or other JAK pathway alterations (NCT02723994). Patients are stratified into cohorts by specific JAK pathway genetic mutations and end of induction MRD responses. The primary endpoint of this nonrandomized trial is 3-year EFS compared to historical controls treated with the same chemotherapy platform alone. The safety phase of this trial was completed with results recently reported [41]. Forty patients enrolled across six dose levels and the recommended phase 2 dose (RP2D) was determined by observed toxicities and inter-cycle delays. While all dose levels were tolerable, there was a trend towards longer inter-cycle treatment delays due to myelosuppression when ruxolitinib was administered continuously, and the 50 mg/m^2/dose BID intermittent (14 days on/14 days off) dose schedule was selected as the RP2D for part 2 of the trial, which is currently underway.

ABL-class fusions (*ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, *PDGFRB, LYN*) comprise approximately 10%–15% of Ph-like ALL in children, and the recently closed COG AALL1131 trial for newly diagnosed high-risk B-ALL included a stratum for patients with a confirmed ABL-class alteration. For patients with the alteration, the ABL1 tyrosine kinase inhibitor, dasatinib, was administered daily in combination with augmented BFM-based chemotherapy post-induction (NCT02883049). Combination therapy was tolerable and the outcomes of this uniformly treated cohort of patients will be analyzed. Similarly, the SJCRH Total XVII trial is investigating ruxolitinib or dasatinib in combination with chemotherapy for children 1–18 years of age with newly diagnosed Ph-like ALL with ABL-class fusions or relevant JAK pathway alterations and persistent mid- or end-induction MRD (NCT03117751).

Molecularly targeted therapy for Ph-like ALL is also being investigated in a number of clinical trials in adults. A tiered approach to screening for Ph-like ALL has been implemented in the current Alliance A041501 clinical trial for adults 18–39 years of age with newly diagnosed ALL. Post-induction, patients who are confirmed to have a *CRLF2* rearrangement or other JAK pathway alteration will potentially be eligible to participate in a companion phase 1 trial combining ruxolitinib with augmented BFM-based chemotherapy (NCT03571321). Similarly, at MD Anderson Cancer Center, children and adults at least 10 years of age with relapsed or refractory Ph-like ALL with targetable alterations are eligible for a phase 1/2 trial investigating dasatinib or ruxolitinib in combination with chemotherapy (NCT02420717).

Given the relative rarity of Ph-like ALL with ABL-class fusions (< 5% of ALL cases overall), future approaches to treatment could include treating these patients on clinical trials for Ph + ALL as well as harmonizing the treatment approaches among the pediatric and adult treating consortia and developing international collaborations. Additional considerations for the future are the roles of MRD and *IKZF1* alterations in risk stratification and treatment allocation. Further, as most ABL-class fusions can be detected rapidly by FISH, another question that remains in this patient subgroup is whether earlier introduction of a TKI in induction will improve early MRD responses and impact outcomes.

Immunotherapeutic approaches

While there is strong rationale for molecularly targeted therapies for Ph-like ALL and several trials are underway, challenges surround this approach too, including the toxicity of combining TKIs with intensive chemotherapy platforms, the emergence of TKI resistance, and persistence of MRD after consolidation. Toxic death rates of up to 15% have been observed when TKIs have been combined with intensive chemotherapy in Ph + ALL [42]. As TKIs are now being used more frequently to treat Ph-like ALL, resistance has also been reported. Zhang and colleagues recently described a novel *PDGFRB* fusion in a patient with Ph-like ALL who initially responded favorably to dasatinib but later developed refractory disease with a point mutation conferring TKI resistance [43]. Finally, the persistence of MRD at the end of consolidation has been associated with very poor outcomes with disease-free survival rates of only 39% in pediatric patients with high-risk B-ALL [44].

Given these challenges, several immunotherapeutic approaches are being explored in Ph-like ALL as well; however, the role of these agents has not been conclusively determined. Adolescent and young adult patients 18–39 years of age with newly diagnosed ALL are currently eligible for the Alliance A041501 trial (NCT03150693), where they receive rituximab if they have CD20-positive disease and they are eligible to participate in a randomization to two cycles of inotuzumab (an antibody-drug conjugate targeting CD22) post-induction. While patients with Ph-like features and JAK pathway alterations may be eligible for enrollment on a companion phase 1 trial investigating ruxolitinib, they remain eligible for treatment on the parent trial where their responses to immunotherapy may be assessed. The COG AALL1732 trial for children, adolescents, and young adults 1–24 years of age with newly diagnosed high-risk B-ALL is anticipated to open this year. Patients may be eligible to participate in a randomization to two cycles of inotuzumab before and after the interim maintenance phase of treatment on this trial. Additionally, patients confirmed to have Ph-like ALL may be eligible for treatment on companion protocols offering targeted therapy.

Promising responses to blinatumomab, a bispecific anti-CD3/CD19 monoclonal antibody, have been observed in adults with persistent MRD after conventional chemotherapy. Seventy-eight percent of adults with B-ALL (including three of five patients with Ph + B-ALL) in hematologic remission with persistent MRD converted to MRD negativity after a cycle of blinatumomab, raising the possibility that these favorable responses will extend to Ph-like disease as well [45]. Two ongoing trials for adults with B-ALL (NCT02003222 and NCT03367299) are investigating the role of blinatumomab in the frontline disease setting. Further, a retrospective study of 12 adult patients with relapsed/refractory Ph + ALL and chronic myelogenous leukemia in lymphoid blast crisis demonstrated that the combination of blinatumomab and a TKI was safe and yielded favorable response rates of 67% [46]. On the SWOG-S1318 trial, older adults with Ph-like ALL with ABL class fusions are eligible to receive blinatumomab in combination with continuous dasatinib (NCT02143414). These trials collectively will offer the opportunity to determine whether immunotherapy alone or in combination with TKIs can improve response rates and outcomes in Ph-like ALL.

Finally, several promising new immunotherapies are also being developed. In *CRLF2*-rearranged ALL, TSLPR forms a heterodimeric complex with IL7R on the cell surface, providing additional potential targets for immunotherapy. Both anti-CRLF2/TSLPR

antibodies and chimeric antigen receptor T-cells targeting TSLPR are currently in development [47,48].

Conclusions

Ph-like ALL is a high-risk subtype of B-ALL that occurs across the age spectrum but with a peak prevalence in adolescents and young adults. Despite the genetic complexity of Ph-like ALL, the majority of cases have alterations involving the ABL or JAK-STAT signaling pathways amenable to approved TKIs. Several diagnostic tests are available to detect the common alterations that define this disease, and new discoveries continue with more comprehensive genomic characterization. Several clinical trials investigating molecularly and immunologically targeted therapy are underway and offer promise for optimizing treatment and outcomes.

Declaration of competing interest

Dr. Maese has no relevant financial relationships with any commercial interest. Dr. Raetz receives institutional research funding from Pfizer.

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