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Philadelphia-like acute lymphoblastic leukemia: diagnostic dilemma and management perspectives

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Acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy characterized by suboptimal outcomes in the adult age group. Recently, a new subtype called Philadelphia (Ph)-like ALL has been described. This subgroup is characterized by high cytokine receptor and tyrosine kinase signaling expression, resulting in kinase activation through stimulation of two main pathways, the ABL and JAK/STAT pathways. The diagnostic method or approach for Ph-like ALL is still not standardized and efforts are ongoing to identify an easy and applicable diagnostic method. Accurate and standard testing approaches are much needed and this will facilitate better understanding of this subgroup, including better estimation of the prevalence and incidence in different age groups and the clinical outcomes of such new entity. Here, we review the currently available diagnostic tools, activated pathways, and different therapeutic approaches used to target this subgroup.

Acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy treated with intensive chemotherapy [1]. In children, ALL therapy was a success story [2]; however, in adults, outcomes remain poor [3]. The poor prognosis of adult ALL is attributed to the accumulation of poor prognostic features, including, but not limited to, the higher frequency of poor-risk genomic subgroups, the lower tolerability to prolonged courses of intensive chemotherapy, and the high therapy-related mortality after hematopoietic cell transplantation (HCT) [4].

A new category of poor-risk ALL, called Philadelphia (Ph)-like ALL, was recently identified [5] and listed as a new provisional category in the World Health Organization 2016 classification [6]. This new group is defined by high expression of cytokine receptors and tyrosine kinase genes with a gene expression profile similar to that of Ph-positive ALL but without the characteristic *BCR-ABL* rearrangement [7]. Ph-like ALL seems to be common in the adult age group (>20%) and apparently carries a poor prognosis with currently available therapies [8]. Within this Ph-like group, several subgroups have been distinguished depending on the altered kinases or cytokine receptors and these alterations will probably guide the choice of therapy to target the affected pathways in a personalized approach [9].

Discovery and diagnosis of Ph-like ALL

In 1999, acute myeloid leukemia (AML) and ALL were shown to have distinct gene expression profiles [10]. In 2002, different gene expression profiles in ALL were linked to certain cytogenetic abnormalities that have an impact on prognosis [11,12]. In 2009, two studies described a new subtype of B-cell ALL (B-ALL) characterized by poor outcomes and by mutations, rearrangements, and copy number alterations involving cytokine receptor or kinase genes other than the *BCR-ABL* fusion. The investigators from the Children's Oncology Group (COG) and St. Jude Children's Research Hospital (SJCRH) called this subgroup Ph-like ALL, whereas the Dutch group called it *BCR-ABL1*-like ALL [5,13,14]. Later on the gene expression profile of this subgroup was shown to be similar to that of Ph-positive ALL [7].

The COG/SJCRH group [14] defined the Ph-like signature based on the prediction analysis of microarrays classifier, which consists of 255 gene probe sets. Using this method, the investigators also showed frequent

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deletions of IKZF1 in this subgroup. However, the Dutch group [5] used a method that relies on hierarchical clustering of 110 gene probes to classify pediatric ALL subtypes (high-hyperdiploidy, mixed-lineage leukemia [MLL]-rearranged, ETV6-RUNX1, TCF3, *BCR-ABL*, etc.). These two gene expression profiling (GEP) methods overlap by nine probe sets and this explains the different definition and incidence of Ph-like/*BCR-ABL1*-like ALL between the two groups [15]. The majority of cases are concordant; however, some cases are discordantly defined as Ph-like by COG/SJCRH and BCR-ABL1-like by the Dutch group [16].

The diagnosis of Ph-like ALL is challenging, but it carries predictive and prognostic implications that help to better define the patient's risk and to personalize the treatment approach based on the presence of targetable mutations. GEP is cumbersome to use in daily clinical practice. Other methods relying on reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or combination of immunophenotyping and DNA sequencing have been used [17,18]. Identifying sensitive and specific algorithms will be very helpful to identify and treat Ph-like ALL in daily clinical practice. Because Ph-like ALL is only found in patients with B-ALL lacking translocation of *BCR-ABL, ETV6-RUNX1, TCF3- PBX1*, or *KMT2A* (*MLL*), Herold et al. developed a flow chart to help in identifying Ph-like ALL based on these facts (Figure 1) [19]. Fasan et al. developed a different diagnostic algorithm based on: (1) analysis of cytokine receptor like factor 2 (*CRLF2*) expression; (2) FISH targeting ABL and Janus activated kinase (JAK) pathway activating fusions involving the genes *ABL1, ABL2, CSF1R, PDGFRB*, and *JAK*; and (3) fusion-specific RT-PCR for identification of the respective *ABL* and *JAK* fusion partner [17]. Another method used by St. Jude uses a 15-gene classifier that could be analyzed on low-density microarray cards [20] and can identify Ph-like ALL with targetable mutations that may respond to tyrosine kinase therapy [8]. Ideally, having a quick, user-friendly, sensitive, and specific diagnostic test or approach (e.g., PCR or FISH in Ph-positive ALL) will help to standardize the diagnostic approach. This will enable us to accurately identify these patients so that they can be enrolled in clinical trials to better define this group and to identify the best therapeutic approach. Eventually, as suggested by some investigators, ALL can be broadly divided into three categories with clearly defined prognosis and therapeutic modality: Ph-positive, Ph-like, and other B-ALL [21].

Epidemiology

The incidence of Ph-like ALL is variable depending on the ethnicity, age group, diagnostic method, and reference group (pre-B-ALL or whole ALL). In one study, 264 of 1725 pre-B-ALL cases (15.3%) among all age groups were labeled as Ph-like ALL [9]. This same study showed that the prevalence of Ph-like ALL increases with age (from 10% among children to 27% among young adults). In another report, Ph-like ALL accounted for 27.9% of young adults (age 21–39 years), 20.4% of adults (age 40–59 years), and 24.0% of older adults (age 60–86 years) [8]. The M.D. Anderson Cancer Center group reported that 49/148 (33.1%) adult patients who underwent gene expression profiling of leukemic cells had Ph-like ALL [21]. Conversely, a large European report showed that the incidence of Ph-like ALL was only 15% of pre-B-ALL cases [16]. These differences are probably due to difference in the ethnicity of the patients and the diagnostic methods used by different groups. Briefly, the incidence of Ph-like ALL seems to be different depending on the age group (seems to be higher in young patients), ethnicity (seems to be higher in Hispanics), and diagnostic method used. Standardizing the diagnostic approach and definition will help us better estimate the incidence of Ph-like ALL.

Genetic alteration and subtypes of Ph-like ALL

ALL is a heterogeneous disease characterized by multiple structural variations, mutations, and chromosomal rearrangements that affect epigenetic regulation and cell growth and proliferation and eventually perturb normal lymphoid maturation [22]. The widespread use of genome sequencing and profiling has shaped our understanding of the genetic basis of ALL and allowed researchers to identify recurring genetic abnormalities and, subsequently, to define new subtypes of ALL such as Ph-like ALL [9]. Based on the altered pathways, patients with Ph-like ALL are subdivided into three main groups: kinase alterations, cytokine receptor alterations, and other less frequent pathway activations such as the RAS pathway) [9,23].

Kinase pathway alteration

The majority of Ph-like ALL cases (90%) have activating kinase alterations [8], particularly deletions of IKAROS Family Zinc Finger 1 (IKZF1), which are found in up to 80% of cases [18]. Normally, IKZF1 is involved in B-cell differentiation [24] and alterations of IKZF1 function portend a poor prognosis in pre-B-ALL [14]. The 5′ part of the fusion transcript leads to constitutive tyrosine kinase activation with no need for receptor stimulation or ligand binding; the 3′ part of the fusion transcript determines the cascade of downstream signal transduction and, potentially, which inhibitors could inhibit the activated cascade and therefore inhibit leukemic cell growth [19,21,25]. ABL gene rearrangements and fusions with different partner genes eventually leading to ABL kinase activation and

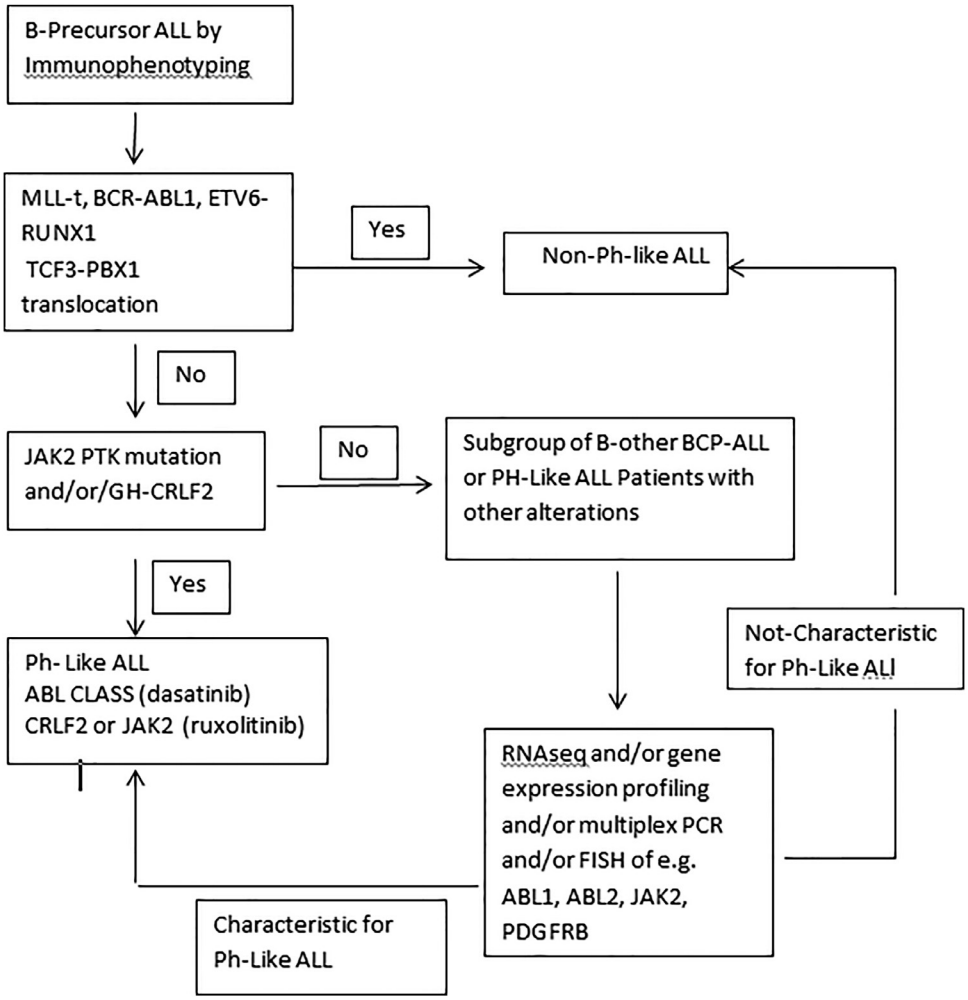

Figure 1. Algorithm for the identification of Ph-like ALL according to Herold et al. (19). PTK, protein tyrosine kinase; RNAseq, RNA sequencing; PCR, polymerase chain reaction; FISH, fluorescence in situ hybridization.

leukemogenesis are also commonly identified in Ph-like ALL cases (9.8–12.6%). Other less common altered kinases include: platelet-derived growth factor receptor (*PDGFR A* and *B*), colony stimulating factor 1 receptor (*CSF1R*), fms-related tyrosine kinase 3 (*FLT3*), diacylglycerol kinase eta (*DGKH*), neurotrophic receptor tyrosine kinase 3 (*NTRK3*), protein tyrosine kinase 2 beta (*PTK2B*), and B-cell linker (*BLNK*) [8,9].

Cytokine receptor pathway alterations

CRLF2 alteration is a frequent abnormality in adult Ph-like ALL (50–60%) and tends to occur in older patients presenting with higher white blood cell count compared with non-CRLF2-rearranged Ph-like ALL. Additionally, CRLF2 appears to cluster in Hispanic patients compared with other ethnicities (78% of patients with CRLF2 overexpression were Hispanic), with the majority of rearrangements involving *IGH-CRLF2* (57.6–76%), followed by *P2RY8-CRLF2* (17–21%) [21]. Rearrangements or sequence mutations of CRLF2 were found exclusively in the Ph-like subgroup [18] and, because it is the most frequent genetic alteration in Ph-like ALL, investigators are now building diagnostic algorithms that include flow cytometric assessment of surface CRLF2 overexpression (thymic stromal lymphopoietin protein receptor, TSLPR), followed by genetic confirmation of specific CRLF2 rearrangements [26,27]. CRLF2-overexpressed cases frequently have coexistent JAK mutation (~47% of patients) and, theoretically, these cases can be targeted by JAK inhibitors [8,28].

Other pathway alterations

Beyond kinase and cytokine receptor alterations, a significant number of Ph-like ALL patients have RAS pathway mutations (KRAS, NRAS, NF1, and BRAF) with downstream activation of the RAF-MEK-ERK kinase axis, a potential target for MEK inhibitors [29–31].

In summary, using delicate genomic methods, the Ph-like ALL can be subdivided into different subgroups [27]. Currently, at least seven subgroups have been described depending on the altered pathway: (1) CRLF2 rearrangements (49.7%); (2) ABL fusions (ABL1, ABL2, CSF1R, and PDGFRB; 12.6%); (3) JAK2 (7.4%) or EPOR (3.9%) rearrangements; (4) genetic alterations of IL7R, FLT3, TYK2, SH2B3, IL2RB, JAK1, JAK3, and other JAK–STAT (12.6%); (5) Ras mutations (4.3%); (6) uncommon fusions (DGKH, NTRK3); and (7) others with no kinase-activating alterations (4.8%) [9]. Table 1 summarizes the frequently affected genes in Ph-like ALL [25].

Clinical characteristics and outcomes

Clinical characteristics

Ph-like ALL is more common in males, with a peak incidence among young adults. Furthermore, patients with Ph-like ALL generally have higher leukocyte counts at presentation compared with patients with non-Ph-like ALL (106,000 vs. 59,000 per cubic millimeter, $p < 0.001$) [8,9]. Two adult studies have confirmed that the incidence of Ph-like ALL was higher (42%) in patients younger than 40 years of age compared with those 40 years or older (24%) ($p = 0.02$) [21]. However, Herold et al. found no significant differences in baseline characteristics, including age, sex, white cell count, hemoglobin, and platelet count, between the Ph-like and remaining pre-B-ALL subgroups [18]. This can potentially be explained by differences in the comparative group between the studies and the differences of criteria used to define Ph-like ALL. Within the Ph-like ALL subgroups, the baseline characteristics seem to be different based on the altered pathway [21]. Table 2 summarizes the clinical characteristics of Ph-like ALL.

Outcomes

ALL is a chemosensitive disease and complete remission rates >90% are universally achieved in all subgroups, including Ph-like ALL; however, maintaining remission is less likely in Ph-like ALL. Increasing age is known to correlate with poor tolerance to chemotherapy and inferior outcomes in all subgroups of ALL and this holds true for Ph-like ALL as well [8]. Several studies from different groups comparing adult and pediatric patients with Ph-like ALL with non-Ph-like ALL patients from the same age group showed lower continuous remission rates, higher relapses, and thus lower survival in the Ph-like group [5,14,15,18,28,32,33]. A study from M.D. Anderson Cancer Center showed that the 5-year overall survival (OS) for Ph-like ALL was significantly lower than that of the non-Ph-like ALL group (23% vs. 59%, $p = 0.006$), except for the MLL-rearranged group, who had a median OS of 10.2 months. This same study showed no difference in the complete remission rate and minimal residual disease (MRD) rate between the Ph-like CRLF2$^+$ and the Ph-like non-CRLF2 group; however, the CRLF2-overexpressed subgroup had significantly inferior OS (5-year survival <20% in the CRLF2$^+$ group), event-free survival, and remission duration compared with other genomic subgroups. Additionally, this study showed that, within the Ph-like group, the IKZF1 deletion did not affect OS, but the

Table 1. Fusion gene rearrangements in Philadelphia like ALL

Inhibitor Type	Fusion Gene	Protein Function	Partner Gene(S)	Type of Fusion
ABL class	ABL1	Tyrosine kinase	ETV6, NUP214, ZMIZ1, RCSD1, NUP153,SFPQ, RANBP2, SNX1, SNX2, SPTAN1, FOXP1	Chimeric protein
	ABL2	Tyrosine kinase	RCSD1,PAG1, ZC3HAV1	Chimeric protein
	PDGFRB	Cytokine receptor tyrosine kinase	EBF1, ATF7IP, SSBP2, TNIP1, ZEB2, SNX29	Chimeric protein
	CSF1R	Cytokine receptor tyrosine kinase	SSBP2, MEF2D	Chimeric protein
	PDGFRA	Cytokine receptor tyrosine kinase	FIP1L1	Chimeric protein
JAK2 class	JAK2	Tyrosine kinase	PAX5, BCR, ATF7IP, EBF1, PPFIBP1, SSBP2,STRN3, TPR, TERF2, ETV6, OFD1, SMU1, ZNF340	Chimeric protein
	EPOR	Cytokine receptor	IGH, IGK, LAIR1, THADA	Overexpression truncated protein
	CRLF2	Cytokine receptor	P2RY8, IGH, CSF2RA	Overexpression
Miscellaneous	TYK2	Tyrosine kinase	MYB, SMARCA4, ZNF340	Chimeric protein
	NTRK3	Cytokine receptor tyrosine kinase	ETV6	Chimeric protein
	FLT3	Cytokine receptor tyrosine kinase	ZMYM2	Chimeric protein
	PTK2B	Tyrosine kinase	TMEM2	Chimeric protein
	IL2RB	Cytokine receptor	MYH9	Overexpression

Table 2. Ph-like ALL clinical characteristics

Variable	Comments
Age	More common in adolescent and young adult
Ethnicity	Common in Hispanic
Gender	Male predominance
Presenting WBCs	Higher counts
Molecular variation	Associated with IKZF1, CRLF2, JAK2, or ABL abnormalities
Response and outcome	Tend to have more induction failure and higher relapse rate
Prognosis	Poor
Therapeutic approach	Trials ongoing to add targeted therapy (targeting the altered pathway) to chemotherapy mirroring the Ph-positive ALL experience (ruxolitinib, TKI, etc.)

JAK2 mutation did affect survival significantly (median OS in JAK2-mutated patients was 18.8 months vs. 26.9 months for patients with wild-type JAK2, $p = 0.012$) [21].

The achievement of deep responses and MRD negativity also seem to be significantly less in the Ph-like subgroup, which translates to higher and earlier relapses after remission induction compared with other ALL subgroups [8,18,21,34]. MRD-guided therapy has been reported to mitigate the prognostic significance of Ph-like ALL in children; however, in adults, the Ph-like ALL outcomes remain poor despite the achievement of MRD negativity [21,35]. In addition to age and MRD status, IKZF1 alteration, NRAS mutation, JAK2 mutation, and CRLF2 rearrangements also correlate with poor overall survival and outcomes [18,21,36,37].

Overall, the outcomes of Ph-like ALL patients are inferior to the outcomes of non-Ph-like ALL patients (except for the MLL-rearranged subgroup), with consistently lower disease-free survival (DFS) and OS [8,9,21].

Management and targeted therapies

Advancements in genome-wide profiling have paved the way to a better and deeper understanding of Ph-like ALL genetic basics and recurrent alterations. These advancements helped investigators to use different pathway inhibitors to target these abnormally activated pathways in a personalized therapy approach. Two main pathways are frequently activated in Ph-like ALL cases, the JAK-STAT and ABL pathways, which makes these patients susceptible to tyrosine kinase inhibitors (TKIs) targeting these pathways [7,9]. Patients with CRLF2 rearrangements frequently (~50%) have point mutations of JAK1 or JAK2, whereas patients with no CRLF2 rearrangements can have JAK2 fusion proteins, carry sequence mutations or copy number alterations activating JAK-STAT signaling (including IL7R, SH2B3, and JAK1) or truncating rearrangements of the erythropoietin receptor (EPOR) and all of these patients are considered JAK activated and are sensitive to ruxolitinib in vitro. Conversely, patients who harbor alterations or fusions involving the ABL-class genes (ABL1, ABL2, CSF1R, and PDGFRB) are sensitive to ABL1 TKIs [8,9,38–47]. In addition, new fusion genes (GATAD2A-LYN fusion) are reported to activate SRC and are sensitive to dasatinib [48,49]. FLT3-activating alterations are also reported in Ph-like ALL and these are sensitive to FLT3 inhibitors [50,51]. A small subgroup of Ph-like ALL patients have no targetable lesions [51]. Imatinib, dasatinib (targeting ABL1, ABL2, CSF1R, and PDGFRB), and ruxolitinib (targeting JAK, CRLF2, and EPOR alterations) showed some activity in preclinical studies and case reports [51,52] and a number of phase II/III prospective clinical trials are recruiting patients to study the effect of ruxolitinib or dasatinib with chemotherapy in patients with Ph-like ALL (NCT02420717, NCT02723994, NCT02883049). Ruxolitinib works by freezing the JAK2 protein in its active, phosphorylated state and carries the risk of rebound activation when ruxolitinib is stopped. Type II JAK2 inhibitors, which inhibit JAK2 in its inactive, nonphosphorylated state, may possibly avoid this rebound effect, although this needs proof of concept [25,53]. There are many new drugs in the preclinical setting for targeting Ph-like ALL pathways. Ruxolitinib and the mammalian target of rapamycin (mTOR) inhibitor rapamycin (sirolimus) were found to be effective against CRLF2 rearrangements with JAK2 mutations [45]. Treatment with the dual phosphoinositide 3-kinase/mTOR inhibitor gedatolisib in murine xenograft models resulted in near eradication of ALL in (CRLF2)/JAK-mutant models [54]. A recent study demonstrated that heat shock protein 90 (HSP90) inhibition using a purine-scaffold HSP90 inhibitor in early clinical development is an effective therapeutic approach in JAK-dependent ALL and can overcome resistance to JAK inhibitor therapy in ALL cells [55]. The histone deacetylase inhibitor givinostat exhibits potent antitumor activity against CRLF2-rearranged ALL by reducing STAT5 phosphorylation [56]. In studies of other tumor models, cells expressing ETV6–NTRK3 responded to the ALK inhibitor

Table 3. Targeted therapies under investigation for Ph-like ALL

Drug	Phase of Clinical Studies Development	Ph-Like ALL Target	Method of Action
Birinapant (TetraLogic)	In vitro and in vivo studies	TNF-α dependent	SMAC mimetic
CHZ868 (Novartis)	In vitro and in vivo studies (not for clinical use)	*JAK2* mutated	Type 2 JAK2 inhibitor
Dasatinib (Bristol-Myers Squibb)	Phase 2 and 3 clinical trials in progress	SRC/ABL class tyrosine kinase fusions	Type 2 SRC/ABL class tyrosine kinase inhibitor
Gedatolisib (Pfizer)	In vitro and in vivo studies	PI3K and mTOR -activated pathways	Dual inhibitor of PI3K-α, PI3K-γ, and mTOR
Givinostat (Italfarmaco)	In vitro and in vivo studies	CRLF2+	Class 1 and class 2 HDAC inhibitor
JQ1 (Roche)	In vitro and in vivo studies	CRLF2+	BET inhibitor
Ponatinib (Ariad)	Single case study	SRC/ABL class tyrosine kinase fusions	Type 3 SRC/ABL class tyrosine kinase inhibitor
Ruxolitinib (Incyte)	Phase 2 clinical trials in progress	*JAK2*-mutated	Type I JAK2 inhibitor
Rapamycin (Pfizer)	In vitro and in vivo studies	mTOR-activated pathways	Inhibitor of mTOR
Luminespib (Novartis)	In vitro and in vivo studies	CRLF2+	HSP90 inhibitor
Selumetinib (Astra-Zeneca) and AZD1480 (InvivoGen)	In vitro studies	CRLF2+	MEK 1/2 inhibitor and ATP-competitive JAK2 inhibitor
TSLPR CAR T cells (National Cancer Institute)	In vitro and in vivo studies	CRLF2+	Allogeneic TSLPR CAR T cells

BET=bromodomain and extra-terminal; CAR=chimeric antigen receptor; HDAC=histone deacetylase; SMAC=second mitochondria-derived activator of caspases; TNF-α=tumor necrosis factor alpha; TSLPR=thymic stromal lymphopoietin receptor

crizotinib [9,57]. Table 3 summarizes the medications under investigation to target the pathways of Ph-like ALL [30].

In Ph-positive ALL, combining targeted therapy along with chemotherapy led to higher and deeper remissions and eventually better DFS and OS compared with chemotherapy alone [58]. Combination therapy trials for Ph-like ALL are the next step and currently being designed. Standard chemotherapy will probably remain a very important component to eliminate the bulk of leukemic cells and to avoid the outgrowth of clones or subclones with alternative activated pathways [25], whereas targeted therapies will probably aid in getting deeper and more sustained remission and as a long-term, low-toxicity maintenance strategy. The guidelines of major organizations such as the American Society for Blood and Marrow Transplantation, the National Marrow Donor Program (http://marrow.org/Physicians/When_to_Transplant/Referral_Guidelines.aspx), and the European Blood and Marrow Transplant Group (https://test.ebmt.org/Contents/Resources/Library/EBMTESHhandbook/Documents/EBMT2008_Cap21.pdf) have no clear recommendations on the use of HCT in patients with Ph-like ALL in CR1. This is partly because this is a new, not well-defined entity and partly because there are no sizable trials addressing this subgroup of patients. However, all major trials addressing the role of allo-HCT in CR1 for ALL patients showed that allo-HCT is the strongest modality available to decrease the relapse rate [3,59–62], so it is reasonable to recommend allo-HCT for Ph-like ALL patients in first complete remission because of the higher relapse rate associated with this subgroup. Obviously, MRD-directed therapy is another reasonable approach to help allocate the highest-risk patients with persistent MRD for allo-HCT.

Molecular genetics perspectives and future directions

Advances in molecular technologies over the past decades helped to characterize the genetic basis of several disorders. Starting with karyotype analysis, which enable scientists to rearrange chromosomes and detect copy number changes, followed by the technology of using the loss of heterozygosity analysis, technologies keep moving forward. Recently, DNA/RNA sequencing resolved many of the most mysterious genomic mutations, including small insertions/deletions, base substitutions, rearrangements, and copy number alterations [11]. In molecular testing, the Sanger sequencing technique is one of the most widely used analysis platforms for mutation detection. The innovation of the gene expression profiling, along with next-generation sequencing (NGS), led to advanced molecular subtyping with a promising future in earlier diagnosis, accurate prognosis, identification of targeted therapies, and eventually disease prevention. Using NGS, a panel of multiple genes could be screened for mutations in a single quick analysis with a considerably low cost through the application of

Table 4. Comparing available diagnostic methods of Ph-like ALL

Method	Advantage	Limitations
FISH	Easily available	Limited to the specific probes and algorithm to follow; may miss many subtypes
Gene sequencing	Can detect all mutations and fusion genes	Expensive and time consuming; not commercial available
Low-density microarray (LDA) cards	quick, user friendly, sensitive and specific diagnostic test	Identifies only targeted mutations; requires frozen tissue

massive parallel sequencing technology [63]. Proteomics have focused on different clinical applications, including identifying candidate biomarkers for diagnosis and early detection of disease, studying the pathogenesis of diseases, increasing the understanding of the mechanism of drug action, and identifying novel drug targets, along with the assessment of safety and efficacy of therapeutic interventions [64–67]. With the availability of these techniques worldwide, including in developing countries, the different or slightly different genetic landscape of Ph-like ALL might surface given the high rate of consanguinity and different lifestyles in different parts of the world. Currently, scientists are able to use high-throughput technologies including genomics, transcriptomics, proteomics, and metabolomics to reveal several diseases' enigmatic secrets including Ph-like ALL. Characterizing the molecular genetic basis of Ph-like ALL at diagnosis by NGS will facilitate rapid, accurate, and cost effective diagnosis, along with identification or predictive and prognostic tools, which will translate into better management of such patients. Table 4 summarizes the currently available diagnostic methods of Ph-like ALL.

Conclusions

Ph-like ALL is a distinct subtype of high-risk ALL with poor prognosis. It is characterized by tyrosine kinase and cytokine receptor signaling gene alterations that lead to kinase activation through activation of two main pathways, the ABL and JAK/STAT pathways. The development of sensitive, cost-effective, standardized, and widely and commercially available diagnostic approaches is much needed in order to better identify these patients and enroll them in the appropriate trials. The incidence and outcomes of this group are poorly understood, in part because this is a relatively new entity, but mainly due to the lack of a well-standardized diagnostic method. Accurately identifying these patients early on during the disease process and enrolling them in trials is of utmost importance to answer some of the many remaining unknowns about Ph-like ALL (e.g., sensitivity to targeted agents, intensity of therapy, importance of combination therapy, value of MRD, necessity for HCT) to optimize the outcomes of this subgroup.

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