BCR/ABL1-Like Acute Lymphoblastic Leukemia: From Diagnostic Approaches to Molecularly Targeted Therapy

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Keywords

BCR/ABL1-like acute lymphoblastic leukemia · Immunophenotype · Cytogenetics · Molecular characteristic · Molecular-targeted therapy

Abstract

Background: *BCR/ABL1*-like acute lymphoblastic leukemia is a newly recognized high-risk subtype of ALL, characterized by the presence of genetic alterations activating kinase and cytokine receptor signaling. This subtype is associated with inferior outcomes, compared to other B-cell precursor ALL.

Summary: The recognition of *BCR/ABL1*-like ALL is challenging due to the complexity of underlying genetic alterations. Rearrangements of *CRLF2* are the most frequent alteration in *BCR/ABL1*-like ALL and can be identified by flow cytometry. The identification of *BCR/ABL1*-like ALL can be achieved with stepwise algorithms or broad-based testing. The main goal of the diagnostic analysis is to detect the underlying genetic alterations, which are critical for the diagnosis and targeted therapy. **Key Messages:** The aim of the manuscript is to review the available data on *BCR/ABL1*-like ALL characteristics, diagnostic algorithms, and novel, molecularly targeted therapeutic options.

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Introduction

B-cell acute lymphoblastic leukemia (B-ALL) is a malignant transformation and differentiation of a clonal population of B-lineage precursor cells within the bone marrow, blood, and extramedullary sites, and is characterized by a wide range of sentinel genetic alterations, including aneuploidy and chromosomal rearrangements [1]. The detailed mechanism of malignant transformation of B-cells remains unknown. The majority of cases carry mutations in genes encoding lymphoid transcription factors, tumor suppressors, cell cycle regulators, and epigenetic modifiers [2, 3]. The presence of cytogenetic and molecular aberrations is now the basis of the updated WHO B-ALL classification, dividing B-ALL into 2 main categories: B-ALL with recurrent genetic abnormalities and B-ALL not otherwise specified. Recurring chromosomal alterations are the distinctive feature of ALL and include aneuploidy, t(12;21) [*ETV6/RUNX1*], t(1;19) [*TCF3/PBX1*], t(5;14) [*IL3/IGH*], t(9;22) [*BCR/ABL1*], and the rearrangement of *MLL* [4]. The prevalence of sentinel genetic aberrations varies within age-groups, contributing to the decline of survivorship with an increase in age [5]. While ALL is the most frequent neoplasm in children with cure rates exceeding 85.0% [6], long-term prognosis for adults remains inferior. According to the

Cancer and Leukemia Group B study, the 3-year overall survival rate varies between younger patients (30–59 years) and the elderly (>60 years), achieving approximately 38.0% and 12.0%, respectively [7]. Among adolescent and adult patients with ALL, the presence of favorable genetic features, including hyperdiploidy and *ETV6/RUNX1*, is less frequent than in children, while the prevalence of unfavorable genetic abnormalities (including *BCR/ABL1*) is higher [8]. Recently, a novel high-risk subtype of B-cell ALL has been identified with a similar gene expression profile to the *BCR/ABL1*-positive ALL. It was first reported in 2009 by Mullighan et al. [9] from the Children's Oncology Group (COG) and St Jude Children's Research Hospital (SJCRH) and by den Boer et al. [10] from Dutch Childhood Oncology Group (DCOG). The newly recognized B-ALL subtype is called *BCR/ABL1*-like or Philadelphia chromosome-like (Ph-like) ALL. It has been included as a provisional entity in the WHO classification [4]. The majority of *BCR/ABL1*-like ALL cases carry alterations in key transcription factors involved in the B-cell development, including IKAROS family zinc finger 1, transcription factor 3 (E2A), early B-cell factor 1, and paired box 5 [11–13]. The incidence of *BCR/ABL1*-like ALL increases with age, accounting for 10.0–15.0% in children, 21.0% in adolescents, 27.0–27.9% in young adults (21–39 years), 20.4% in adults (40–59 years), and 24.0% in older adults (>60 years) [11, 14, 15]. *BCR/ABL1*-like subtype is associated with inferior outcomes, compared to other B-cell precursor ALL (BCP-ALL): *BCR/ABL1*-negative and non-*BCR/ABL1*-like ALL. Patients with this subtype have a higher risk of relapse, lower 5-year event-free survival rates, and overall survival rates. *BCR/ABL1*-like ALL is also associated with a high rate of nonresponse to first-line treatment, high relapse rate, and persistent minimal residual disease (MRD), compared to other BCP-ALL [14, 16–18]. *BCR/ABL1*-like ALL patients have higher WBC counts at the moment of diagnosis in comparison with other BCP-ALL patients [14].

Molecular Characteristic of *BCR/ABL1*-Like ALL

Genetic alteration-activating kinase and cytokine receptor signaling are the hallmark of *BCR/ABL1*-like ALL [11, 16]. Kinase-activating genetic abnormalities can be categorized into several classes. These include rearrangements of cytokine receptor-like factor 2 (*CRLF2*) gene, V-abl Abelson murine leukemia (*ABL*) viral oncogene homolog gene-class fusions (*ABL1*, *ABL2*, *CSF1R*, *PDG-*

FRB, *PDGFRA*), Janus kinase 2 (*JAK2*) gene, erythropoietin receptor (*EPOR*) gene rearrangements, JAK/STAT-activating aberrations, Ras pathway mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*), and other uncommon fusions (*NTRK3*, *PTK2B*, *BLNK*, *FLT3*) [11, 14, 19, 20]. The rearrangements of *CRLF2* remain the most frequent alteration in *BCR/ABL1*-like ALL. Approximately, 35.7–75.0% of *BCR/ABL1*-like ALL patients have *CRLF2* overexpression [18, 21, 22]. *CRLF2* encodes the thymic stromal lymphopoietin receptor (TSLPR). It heterodimerizes with interleukin-7 receptor alpha chain and leads to induction of JAK/STAT, Ras/MAPK, and PI3K/Akt/mammalian target of rapamycin (mTOR) pathway signaling and lymphoid development. *CRLF2* is located in the pseudoautosomal region 1 on the Xp22.3 and Yp11.3 chromosomes [23]. Overexpression of *CRLF2* occurs as a consequence of either translocation juxtaposing *CRLF2* to the immunoglobulin heavy chain locus or an intragenic deletion of the pseudoautosomal region 1 of chromosomes X and Y (*P2RY8-CRLF2*) [23, 24]. Less frequently, activating point mutations (most often p.Phe232Cys) are present [25]. Although the rearrangements of *CRLF2* are the most common alteration in *BCR/ABL1*-like ALL, approximately 5.0–10.0% of *CRLF2*-rearranged ALL cases are not *BCR/ABL1*-like ALL, since the gene expression signature lacks genetic alteration-activating tyrosine kinase signaling [26]. What is more, the diagnosis of *BCR/ABL1*-like ALL is challenging due to a possible concurrence of *CRLF2* and *BCR/ABL1* rearrangements [27]. According to Meyer et al. [28], *BCR/ABL1*-like ALL blasts with *CRLF2* rearrangements demonstrate reduced sensitivity to glucocorticoids in vitro, which could be partially responsible for poor therapy outcomes. The overexpression of *CRLF2* is associated with unsatisfactory response to chemotherapy and poor outcomes even in non-*BCR/ABL1*-like cases [22, 29]. What is more, among *BCR/ABL1*-like ALL patients, *CRLF2*-rearranged cases carry the worst prognosis [18]. It was confirmed that approximately 50.0% of these cases harbor mutations in the *JAK* family genes, most frequently in *JAK2*, rarely in *JAK1* and *JAK3* [11, 22, 25]. Activating point mutations within *JAK2* occur in different locations than V617F. The most recurrent alteration is R683G [13, 30]. The concomitance of *CRLF2* overexpression and *JAK2* mutations is associated with inferior outcomes [11, 17]. Less frequently, gain-of-function somatic mutations (c.642A>T, c.814ins13delA, c.819ins12, c.820ins21, c.828ins7delT) within the interleukin-7 receptor alpha chain have been observed in the *CRLF2*-rearranged leukemias [31]. Several preclinical studies have shown that *CRLF2*-rearranged leukemias and leukemias

Fig. 1. The results of a diagnostic work-up of a 21-year-old patient with *CRLF2*-rearranged *BCR/ABL1*-like ALL. **a** Peripheral blood smear. Blasts (pointed with arrows) with scant cytoplasm, dispersed nuclear chromatin, and prominent nucleoli. Wright's stain ($\times 100$ magnification). **b** Bone marrow aspirate smear. Blasts are pointed with arrows. Wright's stain ($\times 20$ magnification). **c** Multicolor FC analysis. Side scatter versus CD45. Violet, blasts. Red, and other cells. **d** Multicolor FC analysis of *CRLF2* expression on leukemic blasts. Violet, *CRLF2*-positive blasts; green, other cells. In the presented case, the 10-color FC (BD FACS Canto II Ilyric™)

analysis revealed: CD13 0.0%, CD33 80%, CD34 94%, CD117 0.0%, HLA DR 99%, CD38 92%, CD31 100%, CD36 0.0%, CD14 0.0%, CD11b 0.0%, CD11c 0.0%, CD64 0.0%, CD163 0.0%, CD18 0.0%, CD56 0.0%, CD16 0.0%, CD19 99%, CD10 97%, CD20 90%, CD22 96%, CD3 0.0%, CD5 0.0%, CD4 0.0%, CD8 0.0%, CD7 0.0%, CD2 0.0%, CD1a 0.0%, CD66b 0.0%, CD66c 0.0%, CD65 0.0%, CD15 77%, CD123 0.0%, *CRLF2* 79%, cytCD68 0.0%, MPO 0.0%, TdT 99%, cytCD3 0.0%, cytCD79a 91%, cytIgM 0.0%, kappa 0.0%, lambda 0.0%, CD45 dim. FSC low, SSC low/mid (personal data). *CRLF2*, cytokine receptor-like factor 2; FC, flow cytometry.

with other JAK pathway alterations are susceptible to JAK inhibitors or a combination of JAK/STAT and mTOR pathway inhibitors [32–34]. Furthermore, overexpression of TSLPR on blast surface may be an immunothera-

peutic target for chimeric antigen receptor T-cells [35, 36]. According to Qin et al. [35], TSLPR may play a significant role in the survival of leukemic cells, since late relapses occur with a retained expression of this cytokine

Table 1. Algorithms used for the identification of the *BCR/ABL1*-like B-ALL [11, 16, 22, 26, 45, 47, 48, 50, 52–55]

Author	Ph-like ALL detection method/algorithm used
Harvey et al. [47]	15-Gene LDA predictor
Heatley et al. [48]	9-Gene LDA predictor
Reshmi et al. [52]	8-Gene LDA predictor
Chiaretti et al. [50]	10-transcript qRT-PCR predictor
Roberts et al. [11]	Stepwise algorithm (LDA, FISH, RT-PCR, NGS)
Fasan et al. [53]	Stepwise algorithm (FISH, RT-PCR, qRT-PCR, NGS)
Roberts et al. [16]	Stepwise algorithm (NGS, RT-PCR)
Jain and Abraham [45]	Stepwise algorithm (FC, FISH, NGS)
Totadri et al. [54]	Stepwise algorithm (qRT-PCR, FC, RT-PCR, FISH, multiplex PCR, MLPA)
Harvey and Tasian [26]	Stepwise algorithm (LDA, FC, FISH, RT-PCR, PCR, NGS, RNA-sequencing)
Sánchez et al. [22]	Targeted RNA-sequencing customized panel of 42 genes
Yap et al. [55]	Targeted RNA-sequencing panel of 13 genes

LDA, low-density array; FISH, fluorescent in-situ hybridization; RT-PCR, real-time polymerase chain reaction; qRT-PCR, quantitative real-time polymerase chain reaction; NGS, next-generation sequencing; FC, flow cytometry; TK, tyrosine kinase; MLPA, multiplex ligation-dependent probe amplification; Ph-like ALL, Philadelphia chromosome-like ALL; B-ALL, B-cell acute lymphoblastic leukemia.

receptor. This finding is in accordance with comparable *CRLF2* expression frequency among patients with de novo and relapsed ALL observed by Konoplev et al. [37]. The second most common kinase pathway alterations within *BCR/ABL1*-like ALL are *ABL*-class fusions, present in approximately 10.0–19.0% of ALL cases, more frequently in children than in adults [11, 19, 20, 26, 38]. According to several studies, patients with *ABL*-class rearrangements may benefit from the addition of tyrosine kinase inhibitor (TKI) – dasatinib to chemotherapy [16, 39, 40]. The rearrangements of *JAK2* and erythropoietin receptor are other commonly observed alterations within *BCR/ABL1*-ALL and occur in approximately 6.5–27.3% and 4.0–6.3% of patients, respectively [14, 20, 41]. Interestingly, the *JAK2* rearrangements are more frequently observed among young adults than children [14].

Immunophenotypic Characteristics of *BCR/ABL1*-Like ALL

Flow cytometry (FC) can facilitate the identification of *BCR/ABL1*-like ALL. Overexpression of TSLPR on blast surface is predictive of *CRLF2*-rearranged ALL and can be identified by FC [42] shown in Figure 1. According to Ohki et al. [43], *BCR/ABL1*-like ALL cases have similar immunophenotype to *BCR/ABL1*-positive ALL. A relatively low expression frequency of aberrant myeloid antigen appears – CD27 and CD66c reaching in 44.0% and

36.4% of cases, respectively [43]. At the same time, Ohki et al. [43] observed relatively high CD45RA and CD99 expression in *BCR/ABL1*-like ALL in 80.0% and 90.9% of cases, respectively. However, the immunophenotypic signature distinctive for *BCR/ABL1*-like ALL has not been established so far [44].

Proposed Algorithms of *BCR/ABL1*-Like ALL Diagnosis

Establishing *BCR/ABL1*-like diagnostic algorithm remains of clinical significance in view of prognostic relevance and the advent of clinical trials of targeted therapy. Unfortunately, the recognition of *BCR/ABL1*-like ALL is a major challenge due to the diversity of underlying genetic alterations. There are 2 ways to facilitate the identification of *BCR/ABL1*-like ALL: stepwise algorithms, which are economical, but require long turnaround time, or broad-based testing, which requires higher cost, but enables rapid recognition of potentially targetable alterations [45]. So far, several stepwise algorithms have been proposed to facilitate the detection of *BCR/ABL1*-like ALL. These include tiered algorithms and targeted fusion/gene panel testing. The targeted approach identifies key fusions associated with *BCR/ABL1*-like ALL. The tiered algorithm allows detecting *BCR/ABL1*-like ALL based on the quantification of selected predictor gene expression, using a low-density array (LDA) or quantitative

real-time polymerase chain reaction (qRT-PCR) followed by sequential genomic profiling [18, 41, 46]. LDA with an array of 15 genes was developed for the first time by Harvey et al. [47], followed by the creation of other predictors with fewer genes by Heatley et al. [48] and Roberts et al. [49]. Chiaretti et al. [50] built a predictor based on qRT-PCR to assess the expression values of ten types of transcripts. Tiered algorithm with TaqMan-based LDA is currently routinely applied by the Children Oncology Group in newly diagnosed high-risk childhood B-ALL [51]. Patients identified positively for *BCR/ABL1*-like ALL gene expression profile undergo subsequent genetic testing to identify associated genetic alterations. Those with high *CRLF2* expression eventually receive an analysis for the presence of *CRLF2* rearrangements and *JAK1/JAK2* mutations. Patients lacking *CRLF2* overexpression undergo multiplex RT-PCR to detect other kinase fusions with subsequent transcriptome sequencing [52]. The St Jude's Children Hospital adopted a different approach, with RNA-sequencing performed within the first 2 weeks of the remission induction. This approach allows early identification of targetable genetic abnormalities and implementation of TKIs [19]. Regardless of the incorporated algorithm, the main goal of the diagnostic analysis is to detect the underlying genetic alterations, since they are critical for the diagnosis, prognosis, and targeted therapy [51]. The proposed algorithms are listed in Table 1. Some recommend performing fluorescent in-situ hybridization (FISH) analysis using *CRLF2* probe in subjects with high expression of *CRLF2* in FC to identify *BCR/ABL1*-like ALL patients. The possible result of the analysis is shown in Figure 2.

Molecularly Targeted Therapy in *BCR/ABL1*-Like ALL

The determination of an optimal therapeutic strategy in *BCR/ABL1*-like ALL is desired, considering poor outcomes in this entity with conventional treatment. Studies by Chiaretti et al. [50] revealed that *BCR/ABL1*-like ALL patients have a significantly lower complete remission (CR) rate and a higher risk of MRD persistence relative to non-*BCR/ABL1*-like ALL patients [21]. Furthermore, *BCR/ABL1*-like patients experience inadequate event-free survival and disease-free survival. In this study, MRD persistence implicated the performance of hematopoietic stem cell transplant (HSCT) in first CR (CR1); hence, significantly more *BCR/ABL1*-like patients underwent HSCT than non-*BCR/ABL1*-like patients. On the other hand, since the benefit of early MRD clearance in *BCR/*

Fig. 2. The results of a diagnostic work-up of a patient with *CRLF2*-rearranged *BCR/ABL1*-like ALL. **a** FISH analysis with *CRLF2* break-apart probe (CytoCell®) in HR B-ALL patient with high *CRLF2* expression on leukemic blasts in FC. In the normal cell, 2 red/green signals (or yellow, Y) are observed (2Y). Cells with 1 green signal and 1 fused red/green signal (1G, 1Y) may carry an intrachromosomal deletion resulting in the presence of *P2RY8-CRLF2* fusion gene (pointed with arrow). **b** Second step analysis with *P2RY8* deletion probe (CytoCell®). In a normal cell, 2 red/green signals (2R, 2G) are expected. Cells with 1 red and 2 green signals (1R, 2G) carry a hemizygous deletion resulting in the presence of *P2RY8-CRLF2* rearrangement (personal data). HR, high risk; *CRLF2*, cytokine receptor-like factor 2; FISH, fluorescent in-situ hybridization; FC, flow cytometry.

ABL1-like ALL patients remains questioned, the researchers consider post-induction therapy intensification, regardless of the MRD response status [56]. It remains debatable whether all adult *BCR/ABL1*-like ALL patients should receive an allogeneic HSCT in the first CR, irrespective of other indications [57]. So far, no rec-

Table 2. Ongoing clinical trials studying the efficacy of the combination of TKIs and chemotherapy in *BCR/ABL1*-like ALL (www.: clinicaltrials.gov, accessed on 2021, Jun 24)

NCT number	Title	Status	Drug	Ages eligible, year	Study phase
NCT03571321	Phase I trial of ruxolitinib in combination with a pediatric-based regimen for AYAs with Ph-like ALL	Recruiting	Ruxolitinib	18–39	Phase I
NCT02420717	A phase I–II study of the combination of ruxolitinib or dasatinib with chemotherapy in patients with Ph-like ALL	Completed	Ruxolitinib and dasatinib	≥10	Phase I–II
NCT02723994	A phase II study of the JAK1/JAK2 inhibitor ruxolitinib with chemotherapy in children with de novo HR <i>CRLF2</i> -rearranged and/or JAK pathway mutant acute lymphoblastic leukemia	Recruiting	Ruxolitinib	1–21	Phase II
NCT03117751	Total therapy XVII for newly diagnosed patients with acute lymphoblastic leukemia and lymphoma	Recruiting	Ruxolitinib	1–18	Phase III
NCT02883049	A phase III randomized trial for newly diagnosed HR B-ALL including a stratum evaluating dasatinib (NSC#732517) in patients with Ph-like TKI-sensitive mutations	Active, not recruiting	Dasatinib	1–31	Phase III
NCT03564470	An open-label, one-arm, multisite trial of precision diagnosis directing target total therapy for adult Ph-like ALL	Unknown	Dasatinib	14–55	Phase III
NCT02143414	Blinatumomab and combination chemotherapy or dasatinib, prednisone, and blinatumomab in treating older patients with acute lymphoblastic leukemia	Suspended	Dasatinib	≥65	Phase II

B-ALL, B-cell acute lymphoblastic leukemia; Ph-like ALL, Philadelphia chromosome-like ALL; *CRLF2*, cytokine receptor-like factor 2; AYAs, adolescents and young adults; HR, high risk; TKI, tyrosine kinase inhibitor.

ommendations on the use of allogeneic HSCT have been established in *BCR/ABL1*-like ALL patients in the CR1 [58]. According to El Fakih et al. [58], this modality should be recommended in CR1, with several factors considered during the evaluation of the candidates. These factors include the MRD status, presence of *CRLF2*, IKAROS family zinc finger 1, and *JAK2* rearrangements, and availability of modern salvage therapies. Studies by Cho et al. [59] indicate that allogeneic HSCT in *BCR/ABL1*-like ALL patients contributes to improved outcomes. The role of post-HSCT maintenance therapy with TKI in MRD-persistent patients remains debatable. It is questioned whether this approach may eradicate MRD and reduce relapse risk. Aldoss et al. [57] presented a case of a favorable outcome in a patient who received single-agent dasatinib after allogeneic HSCT. Moreover, in view of underlying molecular changes in *BCR/ABL1*-like ALL, the incorporation of TKIs into the therapy regimen is of considerable interest. The results of several preclinical studies signaled the activity of ABL-class inhibitors and JAK inhibitors in ABL-class mutant and JAK pathway mutant *BCR/ABL1*-like ALL, respectively [11, 16, 34, 60, 61]. Jain et al. [62] observed partial downregulation of JAK-STAT signaling in relapsed/refractory *CRLF2*-rearranged patients who received ruxolitinib in combination

with chemotherapy. Studies of Böhm et al. [63] proved that the addition of ruxolitinib to induction therapy with vincristine, dexamethasone, and L-asparaginase increased the in vivo effect in the *CRLF2*-rearranged *BCR/ABL1*-like ALL xenografts. Promising outcomes of TKIs utilization were also reported by Roberts et al. [64]. They demonstrated the cytostatic effect of dasatinib and ruxolitinib monotherapy in *BCR/ABL1*-like ALL harboring ABL-class fusions and JAK-STAT-activating aberrations, respectively. Furthermore, a combination with dexamethasone enhanced this effect [64]. Since single-agent therapy with TKIs in *BCR/ABL1*-like ALL results in limited efficacy, a combination with other agents is under investigation. Studies by Gotesman et al. [40] and Tasian et al. [60] demonstrated that the addition of a mTOR inhibitor enhanced the antileukemic effect of TKIs. Single case reports showed clinical efficacy of a combination of ruxolitinib with chemotherapy in patients with chemoresistant *BCR/ABL1*-like ALL [32, 65]. On the other hand, a recently published case report by Byram et al. [66] showed successful management of a child with relapsed *BCR/ABL1*-like ALL with high-dose ruxolitinib in monotherapy, followed by haploidentical HSCT. There are also several anecdotal reports revealing encouraging results of dasatinib in *BCR/ABL1*-like ALL [39, 67–70]. Currently,

several proceeding clinical trials are evaluating the safety and potency of the addition of dasatinib or ruxolitinib to standard chemotherapy in patients with *BCR/ABL1*-like ALL. Ongoing clinical studies are listed in Table 2. A synergistic effect of TKIs with B-cell lymphoma 2 inhibitors (e.g., venetoclax and navitoclax) was reported by Roberts et al. [64]. Both drugs promote apoptosis and demonstrate antitumor activity in ALL models in the preclinical studies. The phase I study using venetoclax and navitoclax in combination with chemotherapy in relapsed/refractory ALL patients revealed promising outcomes with in all genomic subtypes, although in kinase-driven subtypes (*BCR/ABL1*-like and *BCR/ABL1*-positive ALL), responses were fewer [71]. Recently presented results of Aldoss et al. [72] demonstrated promising outcomes of novel therapies for relapsed/refractory *BCR/ABL1*-like ALL, including blinatumomab (a Bi-Specific Anti-CD19/CD3 BiTE® Antibody), inotuzumab ozogamicin (humanized monoclonal anti-CD22 antibody), chimeric antigen receptor T-cell therapy, and venetoclax-navitoclax anti-B-cell lymphoma 2 therapy [72]. According to the authors' opinion, these therapies could improve the *BCR/ABL1*-like ALL treatment results by reducing disease chemoresistance.

Conclusions

BCR/ABL1-like ALL is characterized by the presence of genetic alteration-activating kinase and cytokine receptor signaling. Underlying molecular changes are complex and often undetectable with standard diagnostic techniques; therefore, identification of this disease subtype remains a clinical challenge. Considering that kinase fusions in *BCR/ABL1*-like ALL contribute to leukemogenesis, and given the inferior outcomes of this entity with conventional chemotherapy, there is a need to estab-

lish an optimal diagnostic and therapeutic approach. Since several clinical studies are currently investigating the addition of molecularly targeted agents to chemotherapy in *BCR/ABL1*-like ALL, the prognosis may improve, similarly to the progress observed in *BCR/ABL1*-positive ALL [73]. Given the fact that results of chemotherapy in *BCR/ABL1*-like ALL patients remain poor, it is believed that *BCR/ABL1*-like ALL patients may benefit from the participation in clinical trials evaluating the efficacy of molecularly targeted therapy based on detailed FC and molecular disease characteristics [60].

Acknowledgments

We would like to thank Kinga Gwóźdz, MSc, for performing blood and bone marrow smear, Jolanta Kiernicka-Parulska, MSc, and Anna Mierzwa, MSc, for the FC data analysis, and Anna Przybyłowicz-Chalecka, MSc, for the FISH study result documentation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Both authors, Anna Płotka and Krzysztof Lewandowski, have contributed significantly to the conception of the manuscript and reviewed the available literature. The manuscript was drafted by Anna Płotka and revised critically by Krzysztof Lewandowski. Both authors approved the final version, and both are accountable for all aspects of the work.

References

- 1 Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J*. 2017 Jun 30;7(6):e577.
- 2 Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. *J Clin Oncol*. 2017 Mar 20;35(9):975–83.
- 3 Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. *Blood*. 2015 Jun 25;125(26):3977–87.
- 4 Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016 May 19;127(20):2391–405.
- 5 Roberts KG. Genetics and prognosis of ALL in children vs adults. *Hematology Am Soc Hematol Educ Program*. 2018 Nov 30;2018(1):137–45.
- 6 Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015 Oct 15;373(16):1541–52.
- 7 Larson RA. Acute lymphoblastic leukemia: older patients and newer drugs. *Hematology Am Soc Hematol Educ Program*. 2005:131–6.
- 8 Stock W. Adolescents and young adults with acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2010;2010:21–9.
- 9 Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med*. 2009 Jan 29;360(5):470–80.
- 10 den Boer ML, van Slegtenhorst M, de Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol*. 2009 Feb;10(2):125–34.

- 11 Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*. 2014 Sep 11; 371(11):1005–15.
- 12 Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008 May 1;453(7191):110–4.
- 13 Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature*. 2007 Apr 12;446(7137):758–64.
- 14 Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Chen IM, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. *J Clin Oncol*. 2017 Feb;35(4):394–401.
- 15 Roberts KG, Pei D, Campana D, Payne-Turner D, Li Y, Cheng C, et al. Outcomes of children with BCR-ABL1-like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. *J Clin Oncol*. 2014 Sep 20;32(27):3012–20.
- 16 Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. *Cancer Cell*. 2012 Aug 14;22(2):153–66.
- 17 Boer JM, Koenders JE, van der Holt B, Exalto C, Sanders MA, Cornelissen JJ, et al. Expression profiling of adult acute lymphoblastic leukemia identifies a BCR-ABL1-like subgroup characterized by high non-response and relapse rates. *Haematologica*. 2015 Jul; 100(7):e261–4.
- 18 Jain N, Roberts KG, Jabbour E, Patel K, Eterovic AK, Chen K, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood*. 2017 Feb 2;129(5):572–81.
- 19 Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome-like acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk*. 2017 Aug;17(8):464–70.
- 20 Owattanapanich W, Rujirachun P, Ungprasert P, Buaboonnam J, Techavichit P. Prevalence and clinical outcome of Philadelphia-like acute lymphoblastic leukemia: systematic review and meta-analysis. *Clin Lymphoma Myeloma Leuk*. 2020 Jan;20(1):e22–9.
- 21 Chiaretti S, Messina M, Della Starza I, Piciocchi A, Cafforio L, Cavalli M, et al. Philadelphia-like acute lymphoblastic leukemia is associated with minimal residual disease persistence and poor outcome. First report of the minimal residual disease-oriented GIMEMA LAL1913. *Haematologica*. 2021 Jun 1;106(6):1559–68.
- 22 Sánchez R, Ribera J, Morgades M, Ayala R, Onecha E, Ruiz-Heredia Y, et al. A novel targeted RNA-Seq panel identifies a subset of adult patients with acute lymphoblastic leukemia with BCR-ABL1-like characteristics. *Blood Cancer J*. 2020 Apr 24;10(4):43.
- 23 Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Calasanz MJ, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. *Blood*. 2009 Sep 24;114(13):2688–98.
- 24 Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, et al. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. *Nat Genet*. 2009 Nov; 41(11):1243–6.
- 25 Yoda A, Yoda Y, Chiaretti S, Bar-Natan M, Mani K, Rodig SJ, et al. Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia. *Proc Natl Acad Sci U S A*. 2010 Jan 5;107(1):252–7.
- 26 Harvey RC, Tasian SK. Clinical diagnostics and treatment strategies for Philadelphia chromosome-like acute lymphoblastic leukemia. *Blood Adv*. 2020 Jan 14;4(1):218–28.
- 27 Thakral B, Jain N, Tang G, Konoplev S, Vega F, Medeiros LJ, et al. From the archives of MD Anderson Cancer Center: concurrent BCR-ABL1 and CRLF2 rearrangements in B-lymphoblast phase of chronic myeloid leukemia. *Ann Diagn Pathol*. 2021 Jun 5;53:151767.
- 28 Meyer LK, Delgado-Martin C, Maude SL, Shannon KM, Teachey DT, Hermiston ML. CRLF2 rearrangement in Ph-like acute lymphoblastic leukemia predicts relative glucocorticoid resistance that is overcome with MEK or Akt inhibition. *PLoS One*. 2019; 14(7):e0220026.
- 29 Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood*. 2019 Apr 4;133(14):1548–59.
- 30 Pastorczak A, Sedek L, Braun M, Madzio J, Sonsala A, Twardoch M, et al. Surface expression of cytokine receptor-like factor 2 increases risk of relapse in pediatric acute lymphoblastic leukemia patients harboring IKZF1 deletions. *Oncotarget*. 2018 May 25;9(40):25971–82.
- 31 Shochat C, Tal N, Bandapalli OR, Palmi C, Ganmore I, te Kronnie G, et al. Gain-of-function mutations in interleukin-7 receptor- α (IL7R) in childhood acute lymphoblastic leukemias. *J Exp Med*. 2011 May 9;208(5):901–8.
- 32 Ding YY, Stern JW, Jubelirer TF, Wertheim GB, Lin F, Chang F, et al. Clinical efficacy of ruxolitinib and chemotherapy in a child with Philadelphia chromosome-like acute lymphoblastic leukemia with GOLGA5-JAK2 fusion and induction failure. *Haematologica*. 2018 Sep;103(9):e427–31.
- 33 Maude SL, Tasian SK, Vincent T, Hall JW, Sheen C, Roberts KG, et al. Targeting JAK1/2 and mTOR in murine xenograft models of Ph-like acute lymphoblastic leukemia. *Blood*. 2012 Oct 25;120(17):3510–8.
- 34 Zhang Q, Shi C, Han L, Jain N, Roberts KG, Ma H, et al. Inhibition of mTORC1/C2 signaling improves anti-leukemia efficacy of JAK/STAT blockade in CRLF2 rearranged and/or JAK driven Philadelphia chromosome-like acute B-cell lymphoblastic leukemia. *Oncotarget*. 2018 Jan 30;9(8):8027–41.
- 35 Qin H, Cho M, Haso W, Zhang L, Tasian SK, Oo HZ, et al. Eradication of B-ALL using chimeric antigen receptor-expressing T cells targeting the TSLPR oncoprotein. *Blood*. 2015 Jul 30;126(5):629–39.
- 36 Davies DM, Maher J. TSLPR: a new CAR in the showroom for B-ALL. *Blood*. 2015 Jul 30; 126(5):567–9.
- 37 Konoplev S, Lu X, Konopleva M, Jain N, Ouyang J, Goswami M, et al. CRLF2-positive B-cell acute lymphoblastic leukemia in adult patients: a single-institution experience. *Am J Clin Pathol*. 2017 Apr 1;147(4):357–63.
- 38 Severson EA, Vergilio JA, Gay LM, Daniel S, Hemmerich AC, Elvin JA, et al. Genomic landscape of adult and pediatric BCR-ABL1-like B-lymphoblastic leukemia using parallel DNA and RNA sequencing. *Oncologist*. 2019 Mar;24(3):372–4.
- 39 Kobayashi K, Miyagawa N, Mitsui K, Matsuo-ka M, Kojima Y, Takahashi H, et al. TKI dasatinib monotherapy for a patient with Ph-like ALL bearing ATF7IP/PDGFRB translocation. *Pediatr Blood Cancer*. 2015 Jun;62(6):1058–60.
- 40 Gotesman M, Vo TT, Herzog LO, Tea T, Mal-lyia S, Tasian SK, et al. mTOR inhibition enhances efficacy of dasatinib in ABL-rearranged Ph-like B-ALL. *Oncotarget*. 2018 Jan 19;9(5):6562–71.
- 41 Boer JM, Steeghs EM, Marchante JR, Boeree A, Beaudoin JJ, Beverloo HB, et al. Tyrosine kinase fusion genes in pediatric BCR-ABL1-like acute lymphoblastic leukemia. *Oncotarget*. 2017 Jan 17;8(3):4618–28.
- 42 Tasian SK, Doral MY, Borowitz MJ, Wood BL, Chen IM, Harvey RC, et al. Aberrant STAT5 and PI3K/mTOR pathway signaling occurs in human CRLF2-rearranged B-precursor acute lymphoblastic leukemia. *Blood*. 2012 Jul 26;120(4):833–42.
- 43 Ohki K, Takahashi H, Fukushima T, Nantomoku T, Kusano S, Mori M, et al. Impact of immunophenotypic characteristics on genetic subgrouping in childhood acute lymphoblastic leukemia: Tokyo Children's Cancer Study Group (TCCSG) study L04-16. *Genes Chromosomes Cancer*. 2020 Oct;59(10):551–61.
- 44 Siegle BJ, Nardi V. Laboratory testing in BCR-ABL1-like (Philadelphia-like) B-lymphoblastic leukemia/lymphoma. *Am J Hematol*. 2018 Jul;93(7):971–7.
- 45 Jain S, Abraham A. BCR-ABL1-like B-acute lymphoblastic leukemia/lymphoma: a comprehensive review. *Arch Pathol Lab Med*. 2020 Feb;144(2):150–5.
- 46 Chiaretti S, Messina M, Foà R. BCR/ABL1-like acute lymphoblastic leukemia: how to diagnose and treat? *Cancer*. 2019 Jan 15;125(2):194–204.

- 47 Harvey RC, Kang H, Roberts KG, Chen I-ML, Atlas SR, Bedrick EJ, et al. Development and validation of a highly sensitive and specific gene expression classifier to prospectively screen and identify B-precursor acute lymphoblastic leukemia (ALL) patients with a Philadelphia chromosome-like ("Ph-like" or "BCR-ABL1-Like") signature for therapeutic targeting and clinical intervention. *Blood*. 2013 Nov 15; 122(21):826.
- 48 Heatley SL, Sadras T, Kok CH, Nievergall E, Quek K, Dang P, et al. High prevalence of relapse in children with Philadelphia-like acute lymphoblastic leukemia despite risk-adapted treatment. *Haematologica*. 2017 Dec;102(12):e490–3.
- 49 Roberts KG, Reshmi SC, Harvey RC, Chen I-M, Patel K, Stonerock E, et al. Genomic and outcome analyses of Ph-like ALL in NCI standard-risk patients: a report from the Children's Oncology Group. *Blood*. 2018 Aug 23; 132(8):815–24.
- 50 Chiaretti S, Messina M, Grammatico S, Piciocchi A, Fedullo AL, Di Giacomo F, et al. Rapid identification of BCR/ABL1-like acute lymphoblastic leukaemia patients using a predictive statistical model based on quantitative real time-polymerase chain reaction: clinical, prognostic and therapeutic implications. *Br J Haematol*. 2018 Jun;181(5):642–52.
- 51 Tran TH, Loh ML. Ph-like acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2016 Dec 2;2016(1):561–6.
- 52 Reshmi SC, Harvey RC, Roberts KG, Stonerock E, Smith A, Jenkins H, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. *Blood*. 2017 Jun 22;129(25):3352–61.
- 53 Fasan A, Kern W, Nadarajah N, Weber S, Schindela S, Schlenther N, et al. Paper: three steps to the diagnosis of adult Ph-like ALL [Internet]. [cited 2021 Jun 16]. Available from: <https://ash.confex.com/ash/2015/web-program/scheduler/Paper79722.html>.
- 54 Totadri S, Singh M, Trehan A, Varma N, Bhatia P. Keeping PACE with Ph positive to Ph-Like detection in B-lineage acute lymphoblastic leukemia: a practical and cost effective (PACE) approach in a resource constrained setting. *Indian J Hematol Blood Transfus*. 2018 Oct;34(4):595–601.
- 55 Yap KL, Furtado LV, Kiyotani K, Curran E, Stock W, McNeer JL, et al. Diagnostic evaluation of RNA sequencing for the detection of genetic abnormalities associated with Ph-like acute lymphoblastic leukemia (ALL). *Leuk Lymphoma*. 2017 Apr;58(4):950–8.
- 56 Aldoss I, Advani AS. Have any strategies in Ph-like ALL been shown to be effective? *Best Pract Res Clin Haematol*. 2021 Mar;34(1):101242.
- 57 Aldoss I, Kamal MO, Forman SJ, Pullarkat V. Adults with Philadelphia chromosome-like acute lymphoblastic leukemia: considerations for allogeneic hematopoietic cell transplantation in first complete remission. *Biol Blood Marrow Transplant*. 2019 Feb;25(2):e41–5.
- 58 El Fakih R, Savani B, Mohty M, Aljurf M. Hematopoietic cell transplant consideration for Philadelphia chromosome-like acute lymphoblastic leukemia patients. *Biol Blood Marrow Transplant*. 2020 Jan;26(1):e16–20.
- 59 Cho H, Kim Y, Yoon J-H, Lee J, Lee GD, Son J, et al. Non-inferior long-term outcomes of adults with Philadelphia chromosome-like acute lymphoblastic leukemia. *Bone Marrow Transplant*. 2021 Apr 6;56:1953–63.
- 60 Tasian SK, Teachey DT, Li Y, Shen F, Harvey RC, Chen IM, et al. Potent efficacy of combined PI3K/mTOR and JAK or ABL inhibition in murine xenograft models of Ph-like acute lymphoblastic leukemia. *Blood*. 2017 Jan 12;129(2):177–87.
- 61 Duployez N, Grzych G, Ducourneau B, Alarcon Fuentes M, Grardel N, Boyer T, et al. NUP214-ABL1 fusion defines a rare subtype of B-cell precursor acute lymphoblastic leukemia that could benefit from tyrosine kinase inhibitors. *Haematologica*. 2016 Apr;101(4):e133–4.
- 62 Jain N, Jabbour EJ, McKay PZ, Ravandi F, Takahashi K, Kadia T, et al. Ruxolitinib or dasatinib in combination with chemotherapy for patients with relapsed/refractory Philadelphia (Ph)-like acute lymphoblastic leukemia: a phase I–II trial. *Blood*. 2017 Dec 7;130(Supplement 1):1322.
- 63 Böhm JW, Sia KCS, Jones C, Evans K, Mariana A, Pang I, et al. Combination efficacy of ruxolitinib with standard-of-care drugs in CRLF2-rearranged Ph-like acute lymphoblastic leukemia. *Leukemia*. 2021 Apr 24.
- 64 Roberts KG, Yang YL, Payne-Turner D, Lin W, Files JK, Dickerson K, et al. Oncogenic role and therapeutic targeting of ABL-class and JAK-STAT activating kinase alterations in Ph-like ALL. *Blood Adv*. 2017 Sep 12;1(20):1657–71.
- 65 Mayfield JR, Czuchlewski DR, Gale JM, Matlawska-Wasowska K, Vasef MA, Nickl C, et al. Integration of ruxolitinib into dose-intensified therapy targeted against a novel JAK2 F694L mutation in B-precursor acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2017 May; 64(5): 10.1002/pbc.26328.
- 66 Bayram N, Yaman Y, Özdielli K, Telhan L, Nepesov S, Bilgen H, et al. Clinical efficacy of ruxolitinib monotherapy and haploidentical hematopoietic stem cell transplantation in a child with Philadelphia chromosome-like relapsed/refractory acute lymphoblastic leukemia. *Pediatr Transplant*. 2021 Jun;25(4):e14024.
- 67 Weston BW, Hayden MA, Roberts KG, Bowyer S, Hsu J, Fedorow G, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. *J Clin Oncol*. 2013 Sep 1;31(25):e413–6.
- 68 Dai HP, Yin J, Li Z, Yang CX, Cao T, Chen P, et al. Rapid molecular response to dasatinib in a pediatric relapsed acute lymphoblastic leukemia with NCOR1-LYN fusion. *Front Oncol*. 2020;10:359.
- 69 Zhang G, Zhang Y, Wu J, Chen Y, Ma Z. Acute lymphoblastic leukemia patient with variant ATF7IP/PDGFRB fusion and favorable response to tyrosine kinase inhibitor Treatment: a case report. *Am J Case Rep*. 2017 Nov 14;18:1204–8.
- 70 Fazio F, Barberi W, Cazzaniga G, Fazio G, Messina M, Della Starza I, et al. Efficacy of imatinib and chemotherapy in a pediatric patient with Philadelphia-like acute lymphoblastic leukemia with Ebf1-Pdgfrb fusion transcript. *Leuk Lymphoma*. 2020 Feb;61(2):469–72.
- 71 Pullarkat VA, Lacayo NJ, Jabbour E, Rubnitz JE, Bajel A, Laetsch TW, et al. Venetoclax and navitoclax in combination with chemotherapy in patients with relapsed or refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. *Cancer Discov*. 2021 Jun 1; 11(6):1440–53.
- 72 Aldoss I, Afkhami M, Yang D, Mokhtari S, Tomasian V, Gu Z, et al. Favorable outcomes after novel therapies for relapse/refractory Philadelphia-like acute lymphoblastic leukemia. *EHA Library*. In [cited 2021 Jul 3]. Available from: <https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325105/ibrahim.aldoss.favorable.outcomes.after.novel.therapies.for.relapse.refractory.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D2%2Asearch%3Dbldatutomomab>.
- 73 de Labarthe A, Rousselot P, Huguier-Rigal F, Delabesse E, Witz F, Maury S, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. *Blood*. 2007 Feb 15; 109(4):1408–13.