Philadelphia Chromosome–Like Acute Lymphoblastic Leukemia: Progress in a New Cancer Subtype

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Abstract: Philadelphia chromosome–like (Ph-like) acute lymphoblastic leukemia (ALL) is a newly described, high-risk subtype of B-cell ALL. It is characterized by a gene expression profile similar to that of Ph-positive ALL; however, the *BCR-ABL1* fusion is not present. The World Health Organization classification of myeloid neoplasms and acute leukemia recently was updated to include the Ph-like or *BCR-ABL1*–like ALL subtype of B-cell ALL as a provisional entity. Unlike Ph-positive ALL, which is characterized by the pathognomonic *BCR-ABL1* fusion, Ph-like ALL is characterized by a multitude of different genetic rearrangements and mutations. In this review, we outline the age-related and geographic incidence of Ph-like ALL, the association with worse clinical outcomes, and early evidence for the use of ruxolitinib (a Janus kinase 2 inhibitor) and dasatinib (a tyrosine kinase inhibitor targeting ABL1).

Introduction

The discovery, refinement, and specific characterization of cancer subtypes form the basis of precision medicine. Molecular characterization of cancer can be helpful for patients by detecting biomarkers for diagnosis or prognosis, or eligibility for reduced or targeted therapies. Increased individualized care through molecular classification has not come without obstacles, however. Problems occur with repeatability, predicting response to currently available treatments, identifying markers of metastasis, and identification of tumor targets for effective directed therapies. These shortcomings are unsurprising, given that subtle changes in the expression of just a few genes can produce a considerable number of downstream effects, which vary considerably from patient to patient and across the course of a disease.[1] In addition, consensus is hampered by differences in study designs, sample sets, data processing, and algorithms.[2,3] Overlap among studies has been achieved, however, through the use of large collaborations.[4,5]

Leukemia was among the earliest of cancers to employ stratification of patients by risk of relapse in order to determine chemotherapy treatment intensity.[6-8] Molecular subtyping in leukemia was introduced in the 1970s with the use of T-cell membrane markers

to determine prognosis.[9] Further advances in molecular classification using chromosome number analysis found the minute chromosome 22, named the Philadelphia chromosome, in chronic myeloid leukemia.[10,11] This recurring chromosomal abnormality was later characterized as the t(9;22) *BCR-ABL1* translocation because it involved the Abelson murine leukemia viral oncogene homolog 1 (*ABL1*) on chromosome 9 and the breakpoint cluster region (*BCR*) gene on chromosome 22.[12,13] The *BCR-ABL1* fusion protein is a tyrosine kinase, an enzyme with the ability to phosphorylate proteins. It is present in approximately 30% to 40% of adults with B-cell acute lymphoblastic leukemia (B-ALL).

Gene expression profiling and next-generation sequencing have advanced clinically meaningful molecular subtyping, holding out promise in disease prevention, earlier diagnosis, a more accurate prognosis, and identification of available targeted therapies. These sequencing techniques have identified new deletions, mutations, and chromosomal rearrangements in ALL.[14,15] A recently described subtype that has been added to the World Health Organization's classification of myeloid neoplasms and acute leukemia is Philadelphia chromosome (Ph)-like ALL.[16] Ph-like ALL is a new B-ALL subtype that is defined by a high expression of tyrosine kinase and cytokine receptor signaling genes and an expression profile similar to that of Ph-positive ALL, but without the *BCR-ABL1* chromosomal rearrangement.[17-19]

Diagnosing Ph-Like ALL

Ph-like ALL was first described in children with B-ALL. The Dutch Childhood Oncology Group identified a probe set, corresponding to 110 genes, produced by hierarchical clustering of known subtypes. In the patients with so-called "B-other" ALL, consisting of those without identifiable cytogenetic features, many clustered with *BCR-ABL1*–positive cases and were considered to have *BCR-ABL1*–like ALL.[17] St Jude Children's Research Hospital and the Children's Oncology Group (COG) identified a probe set, corresponding to 257 genes, that identified high-risk *BCR-ABL1*–positive patients using the prediction analysis for microarrays (PAM) method. They found that the IKAROS zinc finger 1 (*IKZF1*) gene not only had significant prognostic influence, it also was present in cases without *BCR-ABL1* translocations. The researchers referred to the patients identified by this probe set as having high-risk *BCR-ABL1*–negative ALL.[18] A signature comparison study, using a cohort of newly diagnosed childhood B-ALL, found intersecting but not identical groups using these 2 independent gene expression classifiers.[20] Both classifiers identified patients with poor outcomes and tyrosine kinase fusion genes. However, only 18% of patients identified as having Ph-like ALL overlapped in both probe sets. This is not unexpected given that there are only 9 overlapping probe sets between the 2 studies owing to different strategies, algorithms, and patient demographics.

TARGET (Therapeutically Applicable Research to Generate Effective Treatments) is a collaboration between COG and the National Institutes of Health (NIH). This initiative developed a 15-gene low-density array (LDA) gene expression card that can be used in the clinical diagnostic laboratory setting using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). The probe sets capture immunoglobulin J polypeptide (*IGJ*), spermatogenesis associated serine rich 2 like (*SPATS2L*), mucin 4 (*MUC4*), cytokine receptor-like factor 2 (*CRLF2*), carbonic anhydrase 6 (*CA6*), neurexin 3 (*NRXN3*), bone morphogenic protein receptor type 1B (*BMPR1B*), G protein-coupled receptor 110 (*GPR110*), chimerin 2 (*CHN2*), semaphorin 6A (*SEMA6A*), paraoxonase 2 (*PON2*), solute carrier family 2 member 5 (*SLC2A5*), S100 calcium binding protein Z (*S100Z*), tumor protein P53 inducible nuclear protein 1 (*TP53INP1*), and interferon induced transmembrane protein 1 (*IFITM1*) gene expression, and identifies more patients with *CRLF2* lesions compared with the original microarray probe set.[21] The LDA card includes probes for the most frequent tyrosine kinase genomic mutations in Ph-like ALL, and is intended for identifying patients who may respond to tyrosine kinase–targeted therapy.[21,22] COG recently used this LDA card in a retrospective analysis, where it proved to be a robust indicator of Ph-like ALL.[23] As a result, COG has implemented this card in its current clinical trial, AALL1131 (NCT02883049).

Incidence and Prognostic Significance of Ph-Like ALL

The incidence of Ph-like ALL differs by geographic location, age, and certain genetic disorders. In Europe, the probe set from the Dutch Childhood Oncology Group was used to identify Ph-like ALL in 13% of adults in the GMALL (German Multicenter Study Group for Adult ALL) cohort[24] and 17% of adults in the HOVON (Dutch-Belgian Hemato-Oncologie voor Volwassenen Nederland) study group.[25] Children enrolled in the German and Dutch trial groups had a 16% incidence of Ph-like ALL. Within that subgroup, 40% had *IKZF1* deletions and 16% had high CRLF2 expression.[26] A Japanese cohort found that 4.7% of B-ALL cases were Ph-like by PCR and 11% by global gene expression analysis using their own clustering algorithms.[27] An Australia and New Zealand Children's Haematology/Oncology Group cohort found an incidence of 10% Ph-like ALL using the LDA card probe set.[28] In the United States, both adolescents and adults have an increased frequency

of Ph-like ALL vs other types of ALL. An analysis of multiple studies of childhood ALL found that Ph-like ALL accounted for 10% of children with standard-risk ALL, 13% of children with high-risk ALL, 21% of adolescents with ALL, and 27% of young adults with ALL using the PAM-derived probe set.[29] Another multicohort study of adult B-ALL found that 27.9% of young adults (ages 21 to 39 years), 20.4% of adults (ages 40 to 59 years), and 24.0% of older adults (ages 60 to 86 years) had Ph-like B-ALL, with classification including the 15-gene LDA.[22] In a smaller US study, 18% of adults older than 40 years with B-ALL were classified as having Ph-like disease.[30]

We previously published results on an adult B-ALL cohort from the MD Anderson Cancer Center (MDACC). We found that of 148 patients, 33.1% had Ph-like ALL.[31] The higher rates of Ph-like ALL seen in the United States can be attributed to both the method of detection—with the LDA array and the PAM-associated probe set possibly capturing a wider patient subset—and also the larger Hispanic population being treated in these cohorts. Hispanic children have been shown to have an elevated risk of developing ALL, and one of the lowest survival rates despite similar therapy regimens.[32] Explanations for Hispanic ethnicity associations with ALL have come from genome-wide association studies that have identified germline GATA binding protein 3 (*GATA3*) mutations, belonging to the GATA family of transcription factors, as a risk factor for ALL with worse outcomes.[33,34] The *GATA3* rs3824662 risk allele was associated with somatic lesions underlying Ph-like ALL (including *CRLF2* rearrangement, Janus kinase [*JAK*] gene mutation, and *IKZF1* deletion).[35,36] It was noted in these studies that Hispanics have one of the broadest genetic ancestry compositions. Native American populations showed similar trends for increased *GATA3* germline mutations, with a much smaller sample cohort. In another study without *GATA3* sequencing data, *CRLF2* rearrangements were significantly associated with Hispanic ethnicity, and this was associated with an increased risk of relapse by univariate but not multivariate analysis in a childhood high-risk B-ALL cohort.[37] The *GATA3* rs3824662 risk allele has been found not only in Hispanic populations but also in a dominant inheritance risk model for B-ALL in an Egyptian cohort of children with ALL.[38] Differences in the probe sets between European and US cohorts may reflect increased numbers of *GATA3* germline mutations, a driver of ALL etiology. Further epidemiologic studies from different genetic backgrounds are needed to gain a better picture of an individual's predisposition to Ph-like ALL.

Regardless, inferior outcomes in patients with Ph-like ALL are seen in both children and adults. In adults, lower rates of continuous complete remission and overall survival were found in Ph-like ALL patients in both Europe[20,39] and the United States compared with other B-ALL subtypes.[22,31] In children, Ph-like ALL patient cohorts from Europe, Japan, Australia, New Zealand, and the United States had poor outcomes, with shorter time to relapse and worse overall survival compared with those in most other B-ALL subtypes.[17,18,28,40] The exceptions were patients with Ph-positive and mixed lineage leukemia (MLL)-rearranged cytogenetics, who had similarly poor outcomes. Childhood Ph-like ALL also was associated with a minimal residual disease level of at least 0.01%.[41] These inferior outcomes have been the main impetus for the expanding studies of Ph-like ALL over the past decade, and for the continual efforts to refine the subtype and characterize it to advance therapeutic benefit.

Molecular Characterization and Classification of Ph-Like ALL

To match the correct patients with potential treatments, there was a need to further classify the Ph-like subtype. Patients were further distinguished by kinase or cytokine receptor genomic alterations that contribute to altered kinase signaling.[29] This molecular classification covers more than 90% of reported cases. The remaining 4% to 10% of cases, depending on age, have no identifiable kinase-activating alteration.[42]

Kinase Alterations

The approval of imatinib for use in patients with *BCR-ABL1*–positive leukemia was followed by the approval of more effective second-generation tyrosine kinase inhibitors.[43,44] Although clinical responses have been impressive with these agents, resistance-inducing mutations and toxic side effects still pose problems.[45] In Ph-like ALL, common kinase fusions targetable by these ABL inhibitors include *ABL1, ABL2*, colony stimulating factor 1 receptor (*CSF1R*), platelet-derived growth factor receptor alfa (*PDGFRA*), and platelet-derived growth factor receptor beta (*PDGFRB*).[29] Other kinase fusions not in the ABL class include diacylglycerol kinase eta (*DGKH*), fms-related tyrosine kinase 3 (*FLT3*), neurotrophic receptor tyrosine kinase 3 (*NTRK3*), protein tyrosine kinase 2 beta (*PTK2B*) and B-cell linker (*BLNK*), which transduces signals from the B-cell receptor and activates the RAS pathway via ERK and casitas B-lineage lymphoma (CBL), a negative regulator of signal transduction pathways.[22,29]

Cytokine Receptor Alterations

Cytokine receptor fusions signal through the JAK/signal transducers and activators of transcription (STAT) pathway. This comprises the membrane-bound thymic stromal lymphopoietin receptor (TSLPR)/CRLF2, which

is functional when the CRLF2 subunit heterodimerizes with the interleukin 7 receptor alfa (IL7RA) subunit.[46] Activation of the TSLPR by TSLP phosphorylates JAKs, which in turn activate various STATs. TSLP stimulation activates AKT serine/threonine kinase 1 (AKT1), extracellular signal–regulated kinase 1/2 (ERK1/2), Jun N-terminal kinases (JNKs), ribosomal protein S6 (RPS6), and eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1). Other *CRLF2*-positive ALL pathways include the phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) pathways.[47] Cytokine receptor–associated alterations that are targetable by JAK2 inhibitors include *CRLF2* (approximately 50%-60% of adult Ph-like ALL cases), *JAK2*, and erythropoietin receptor (*EPOR*) gene rearrangements, all of which lead to increased JAK/STAT signaling.[22,31,48]

Patients with *CRLF2* alterations do particularly poorly. A COG study on childhood ALL found that high *CRLF2* expression in high-risk ALL patients was associated with worse survival.[37,41] *CRLF2* overexpression has been associated with relapse and poor outcome in non–Ph-positive patients.[37,49-51] Even moderate expression of *CRLF2* as detected by flow cytometry has been associated with an increase in phosphorylation of STAT5.[52] The overwhelming majority of patients with *CRLF2* overexpression have 1 of 2 fusion genes: purinergic receptor P2Y, G-protein coupled, 8 (*P2RY8*)-*CRLF2* and immunoglobulin heavy chain locus (*IGH*)-*CRLF2*. *IGH-CRLF2* is more common than *P2RY8-CRLF2* in adults, whereas both the *P2RY8-CRLF2* and *IGH-CRLF2* fusion are found equally in children.[31,53] *P2RY8-CRLF2* has been associated with worse overall survival, but when present as a minor subclone, the fusion was not shown to be responsible for relapse in patients.[51,54] Additional cytokine receptor–related genes involved in Ph-like ALL fusion include interleukin 2 receptor subunit beta (*IL2RB*) and tyrosine kinase 2 (*TYK2*). In an adult cohort, 45% of patients with CRLF2 overexpression also had a *JAK2* mutation.[31] Gain of function mutations in *CRLF2* also have been reported in adults, and to a lesser extent in children, who harbor a concomitant *CRLF2* fusion.[31,53] Additional mutations have been found in *JAK1*, *JAK3*, *IL7R*, and SH2B adaptor protein 3 (*SH2B3*).[29]

CRLF2 alterations and *JAK* mutations are highly correlated with the presence of *IKZF1* alterations, a zinc finger transcription factor required for normal lymphoid development.[37,55] It is unclear from previous studies whether the presence of *IKZF1* alterations leads to worse outcomes across all B-ALL subtypes. There is definitely a correlation between increased *IKZF1* alterations and higher rates of relapse, including increased minimal residual disease in the Ph-like subtype, but whether *IKZF1* has a causative role remains unknown.[19,26,37,49,56-58]

Down syndrome is a genetic disorder involving trisomy of chromosome 21. It has been associated with an increased risk of B-ALL, including an increased risk of Ph-like ALL.[59,60] In the retrospective Ponte Di Legno study covering 16 international trials, *CRLF2* and *JAK2* mutations were found to be common in people with Down syndrome and ALL. The *P2RY8-CRLF2* fusion accounted for more than 90% of observed *CRLF2* rearrangements owing to deletion of the pseudoautosomal region 1 of chromosomes X and Y.[61] Among patients with Down syndrome, those who had *CRLF2* gene rearrangements were younger than those with wild-type *CRLF2.* This age difference was not seen in patients without Down syndrome who had *CRLF2* rearrangements. A previous study had also identified *P2RY8-CRLF2* fusions in 53% of patients with Down syndrome–associated ALL vs 7% of those with ALL that was not associated with Down syndrome.[62] The risk of ALL relapse was higher in patients with Down syndrome in the study. This was largely attributed to treatment-related mortality, however, and *CRLF2* gene rearrangements did not have a significant association with any survival or relapse outcomes. This is in contrast to studies of patients with ALL that is not associated with Down syndrome.[53,63]

Beyond kinase and cytokine receptor alterations, a subset of patients with *RAS* mutations also have Ph-like ALL. These patients may have mutations in *KRAS*, *NRAS*, neurofibromin 1 (*NF1*), protein tyrosine phosphatase, non-receptor type 11 (*PTPN11*), and *BRAF*.[29] Novel fusions continue to emerge from the literature. An example is a *LDLRAD4-PHACTR3* fusion—involving low-density lipoprotein receptor class A domain containing 4 (*LDLRAD4*) encoding a negative regulator of transforming growth factor beta (TGF-β) protein signaling and phosphatase and actin regulator 3 (*PHACTR3*).[64] Also a paired box 5 (*PAX5*) rearrangement with kinase D-interacting substrate of 220 kDa (*KIDINS220*).[65]

Tyrosine Kinase Inhibitors and Other Targeted Therapies

The first drugs to be tested for Ph-like ALL were tyrosine kinase inhibitors targeting SRC/ABL. Clinical evidence of targeted therapy response in case studies of patients with Ph-like ALL and preclinical studies led to phase 2 and 3 clinical trials using dasatinib (Sprycel, Bristol-Myers Squibb) and the JAK2 inhibitor ruxolitinib (Jakafi, Incyte Corporation).

Imatinib is a first-generation ABL kinase inhibitor that binds to the active and inactive conformations of the ABL kinase domain. In contrast, dasatinib is a second-generation ABL kinase inhibitor that binds the inactive and

active conformation of the ABL kinase domain with greater affinity and fewer contact points.

In one case, dasatinib combined with chemotherapy produced complete and ongoing remission in a child with Ph-like ALL who had an activating transcription factor 7 interacting protein (*ATF7IP*)-*PDGFRB* translocation.[66] Two case studies both with young patients harboring an *EBF1-PDGFRB* fusion showed complete remission after treatment with imatinib in combination with conventional chemotherapy.[67,68] In another case, an older patient with Ph-like ALL who had an *ETV6-ABL1* rearrangement had an initial response to dasatinib, followed by a relapse with an ABL1 T315I mutation (this was previously discovered as a resistance mutation in patients with *BCR-ABL1*–positive disease).[69] In another case, an adolescent patient with Ph-like ALL who had an *RCSD1-ABL1* translocation was treated with the third-generation tyrosine kinase inhibitor ponatinib (Iclusig, Ariad). Ponatinib was selected through drug response profiling ex vivo and in patient-derived xenograft models, and the patient achieved clinical remission before relapsing after a hematopoietic stem cell transplant.[70] In a final case, another adolescent with Ph-like ALL who had a *JAK2* mutation was given combined chemotherapy with ruxolitinib, a JAK2 inhibitor that was previously approved for polycythemia vera and myelofibrosis, and achieved negative minimal residual disease before hematopoietic stem cell transplant and long-term remission.[71] Ruxolitinib in this case was delivered at 40 mg/m^2 per day, given twice a day for 2 weeks on and 2 weeks off. The agent was introduced during the interim maintenance phase of high-dose conventional chemotherapy.

Based on these early successes, current clinical trials are identifying Ph-like ALL genetic lesions known to confer susceptibility to either ruxolitinib or dasatinib or by CRLF2 positivity by flow cytometry (for the ruxolitinib cohort). Two current clinical trials are assessing the effectiveness of ruxolitinib: a 2-armed MDACC trial of chemotherapy in combination with either ruxolitinib or dasatinib in patients aged 10 years and older who have Ph-like ALL,[72] and a COG study of ruxolitinib plus chemotherapy in children aged 1 to 21 years who have Ph-like ALL (AALL 1521).[73]

Other active trials in Ph-like ALL include 2 trials from the National Cancer Institute. In the first trial, patients from age 1 to 30 years with newly diagnosed high-risk B-ALL and tyrosine kinase inhibitor–sensitive Ph-like mutations are receiving dasatinib and combination chemotherapy (COG AALL1131).[74] In the second trial, adults aged 65 or older with dasatinib-sensitive mutations or kinase fusions involving *ABL1, ABL2, CSF1R, PDGFRB, PDGFRA*, and fibroblast growth factor receptor (*FGFR*) are receiving dasatinib.[75]

In the preclinical setting, there are still new drugs and strategies being tested for targeted Ph-like therapy (Table).

Preclinically, both ruxolitinib and the mTOR inhibitor rapamycin were found to be effective single agents against *CRLF2* rearrangements with *JAK2* mutations, and against 1 *JAK1* mutation without a *CRLF2* rearrangement. This supports the idea that *JAK*-mutated Ph-like ALL may act through the same JAK/STAT pathways regardless of CRLF2 status.[76] However, other studies have shown in vitro that ruxolitinib, while inhibiting STAT5 phosphorylation, can leave mutated *JAK2* in a constitutively active state of hyperphosphorylation.[77] CHZ868 was developed as an improved, type 2 JAK kinase inhibitor that can better target JAK2 and bind the inactive state. CHZ868 has shown in vitro and in vivo success in models that proved refractory to ruxolitinib, and was proven to completely downregulate phosphorylation of JAK2 and STAT5 and downstream c-MYC, with a marked improvement in both potency and selectivity over other JAK2 inhibitors.[78] This breakthrough will hopefully lead to clinical compounds with similar properties.

Gedatolisib, a dual PI3K/mTOR inhibitor, showed efficacy in vivo in mice engrafted with both *CRLF2* and *ABL*-like fusions, as a single agent and in combination with ruxolitinib or dasatinib.[79] Another Ph-like ALL study targeting multiple pathways found synergy of a MEK inhibitor, selumetinib, and a JAK2 inhibitor, AZD1480, in vitro. This synergy did not translate to the patient-derived xenograft setting, however, because the sustained target inhibition required was not achievable in vivo using tolerable drug dosing.[80]

More recent targets that can suppress the JAK/STAT pathway downstream of CRLF2 include an inhibitor of heat shock protein 90 (HSP90) called luminespib (previously NVP-AUY922). Luminespib leads to the degradation of JAK2, and can more potently suppress JAK/STAT, MAP kinase, and AKT signaling than the type 1 JAK2 inhibitor BVB808. Luminespib was used in vivo on CRLF2-expressing patient-derived xenografts and showed modest prolonged survival.[77,81] Birinapant, a second mitochondria-derived activator of caspases (SMAC) mimetic that can induce apoptosis by inhibiting the activity of cellular inhibitor of apoptosis protein 1/2 (cIAP1/2), has shown anti-leukemic activity in B-ALL PDX models both as a single agent and in combination with chemotherapy. The most acute sensitivity to birinapant was seen in the Ph-like ALL subtype, and was dependent on tumor necrosis factor alfa (TNF-α) expression.[82]

Another potential therapy targeting CRLF2 expression is epigenetic inhibitors. JQ1, an inhibitor of the bromodomain and extraterminal (BET) family of bromodomain proteins, was found to downregulate

Table. Current Investigated Therapies for Ph-Like Leukemia

Drug (Developer)	Ph-Like ALL Target	Method of Action	Preclinical Studies	Clinical Studies
Dasatinib (Bristol-Myers Squibb)	SRC/ABL class tyrosine kinase fusions	Type 2 SRC/ABL class tyrosine kinase inhibitor		Phase 2 and 3 clinical trials in progress (NCT02420717,[72] NCT02883049,[74] and NCT02143414[75])
Ponatinib (Ariad)	SRC/ABL class tyrosine kinase fusions	Type 3 SRC/ABL class tyrosine kinase inhibitor		Single case study[70]
Givinostat (Italfarmaco)	CRLF2+	Class 1 and class 2 HDAC inhibitor	In vitro and in vivo studies[84]	
JQ1 (Roche)	CRLF2+	BET inhibitor	In vitro and in vivo studies[83]	
Luminespib (Novartis)	CRLF2+	HSP90 inhibitor	In vitro and in vivo studies[77,81]	
Selumetinib (Astra-Zeneca) and AZD1480 (InvivoGen)	CRLF2+	MEK 1/2 inhibitor and ATP-competitive JAK2 inhibitor	In vitro studies[80]	
TSLPR CAR T cells (National Cancer Institute)	CRLF2+	Allogeneic TSLPR CAR T cells	In vitro and in vivo studies[86]	
Ruxolitinib (Incyte)	*JAK2*-mutated	Type I JAK2 inhibitor		Phase 2 clinical trials in progress (NCT02420717[72] and NCT02723994[73])
CHZ868 (Novartis)	*JAK2*-mutated	Type 2 JAK2 inhibitor	In vitro and in vivo studies (not for clinical use)[78]	
Rapamycin (Pfizer)	mTOR-activated pathways	Inhibitor of mTOR	In vitro and in vivo studies[76]	
Gedatolisib (Pfizer)	PI3K and mTOR-activated pathways	Dual inhibitor of PI3K-α, PI3K-γ and mTOR	In vitro and in vivo studies[79]	
Birinapant (TetraLogic)	TNF-α–dependent	SMAC mimetic	In vitro and in vivo studies[82]	

ABL, Abelson murine leukemia viral oncogene homolog; ALL, acute lymphoblastic leukemia; BET, bromodomain and extraterminal; CAR, chimeric antigen receptor; CRLF2+, cytokine receptor-like factor 2–positive; HDAC, histone deacetylase; JAK2, Janus kinase 2; mTOR, mammalian target of rapamycin; Ph-like, Philadelphia chromosome–like; PI3K, phosphoinositide 3-kinase; SMAC, second mitochondria-derived activator of caspases; TNF-α, tumor necrosis factor alfa; TSLPR, thymic stromal lymphopoietin receptor.

transcription of interleukin 7 receptor (*IL7R*), a heterodimer of CRLF2, and reduce JAK2 and STAT5 phosphorylation.[83] JQ1 was an effective agent against a *P2RY8-CRLF2*–rearranged Ph-like ALL in vivo. Another epigenetic targeted drug, the histone deacetylase (HDAC) inhibitor givinostat, was used in a *CRLF2*-rearranged leukemia, with or without *JAK2* mutations, and was found to effectively reduce STAT5 phosphorylation and reduce leukemia burden in vivo.[84] New therapies that are highly specific to CRLF2 expression have also been developed. These include a CRLF2 antibody–armored biodegradable nanoparticle designed to deliver a drug payload.[85] Another development is an immune strategy that uses an adoptive transfer of T cells that have been genetically modified to express the anti-TSLPR chimeric antigen receptor.[86] These new therapeutic strategies may prove to have better efficacy than the tyrosine kinase inhibitors that have already moved to clinical trials in Ph-like ALL. However, further validation of their safety, specificity, and activity is needed.

Conclusions

Ph-like ALL is a high-risk subgroup of B-ALL that is seen in approximately 20% to 30% of adolescents and adults with B-ALL. With the use of chemotherapy, outcomes of patients of all ages with Ph-like ALL are significantly inferior to those of patients without the Ph-like gene expression signature. JAK inhibitors and ABL kinase inhibitors are being investigated in clinical trials in patients with Ph-like ALL. The addition of Ph-like ALL to the already known cytogenetic subgroups of ALL is another step toward personalized medicine in the context of treatment of B-ALL.

Disclosures

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