Minireview

Update on BCR-ABL1-like precursor B-cell acute lymphoblastic leukemia

Parvez M. Lokhandwala[1] and Yi Ning[1,*]

[1]Division of Molecular Pathology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, U.S.A.

Abstract: Precursor B-cell acute lymphoblastic leukemia (B-ALL) is the most common type of leukemia in children and young adults. Our understanding of the genetic basis of B-ALL has greatly improved in recent years. Application of genomic profiling and sequencing has led to the identification of a clinically important subgroup of B-ALL patients who are *BCR-ABL1* negative, but exhibit a gene expression profile similar to that of *BCR-ABL1*-positive ALL. This new subgroup has been referred to as *BCR-ABL1*-like ALL. Like *BCR-ABL1*-positive ALL, *BCR-ABL1*-like ALL patients are in the high-risk category, associated with poor outcome. The *BCR-ABL1*-like patients have a diverse range of genetic alterations that activate tyrosine kinase signaling. The recurrent genetic changes include ABL class- or JAK pathway-associated translocations and *IKZF1* deletions. Herein, we review the recent progress in *BCR-ABL1*-like ALL, the recurrent genetic alterations seen in these patients, and the therapeutic potential of targeting the identified molecular changes.

Keywords: ALL, *BCR-ABL1*-like, Ph-like, ABL-rearrangements, JAK2-rearrangements, *IKZF1*

Introduction

Current World Health Organization (WHO) classification recommends that the diagnosis of hematologic malignancies should be based on morphology, immunophenotyping, clinical parameters, and increasingly on the underlying genetic alterations [1]. Genetic and cytogenetic abnormalities have been associated with unique biological, clinical, and prognostic features and, accordingly, define subgroups of hematologic malignancies. Specific genetic abnormalities have been used as independent predictors of disease progression and survival and also to help the classification of challenging types of leukemia [2].

Precursor B-cell acute lymphoblastic leukemia (B-ALL) is the most common type of leukemia in children and young adults. It is well-known that genetic alterations are associated with clinical outcome. Hyperdiploidy and cryptic t(12;21) translocation resulting in *ETV6-RUNX1* fusion are associated with a favorable outcome. Hypodiploidy with less than 44 chromosomes, translocation t(9;22) leading to *BCR-ABL1* fusion, rearrangement involving *MLL*, and intrachromosomal amplification of chromosome 21 are associated with high-risk clinical features or a poor outcome [3, 4].

In this inaugural issue of *Hematopathology*, we would like to briefly review recent progress in

*Correspondence: Yi Ning, PhD, Division of Molecular Pathology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21287; E-mail: yning5@jhmi.edu

BCR-ABL1-like ALL. This progress defines a new subgroup of B-ALL, and also provides therapeutic promises to this high-risk subgroup of patients.

Genetic Basis

Genetic subtypes of ALL are used to determine risk and treatment of childhood ALL. However, approximately 25% of precursor B-ALL cases are genetically unclassified. In order to further improve prognostic classification of ALL, Den Boer *et al*. [5] constructed a classification scheme based on gene expression profile in patients with newly diagnosed ALL. They reported a new ALL subtype with a gene expression profile similar to that of *BCR-ABL1*-positive ALL that was similarly associated with a poor prognosis. Significantly, the number of patients with *BCR-ABL1*-like disease was more than five times the number of *BCR-ABL1*-positive disease, representing the most common subtype of ALL with poor prognosis.

Subsequent studies revealed that in *BCR-ABL1*-like ALL, or Philadelphia chromosome-like (Ph-like) ALL, harbor a diverse range of genetic alterations that activate tyrosine kinase signaling [6, 7]. They are characterized by activation of either the ABL class- or JAK- associated signaling pathways. While the ABL class kinases (ABL1, ABL2, CSF1R, and PDGFRB) are products of fusion genes, the JAK pathway can be activated through gene fusions, mutations, or deletions, including rearrangements of JAK2, CRLF2, EPOR, and mutations of *JAK1*, *JAK2*, *JAK3*, and *IL7R* [8, 9].

ABL Class- and JAK Pathway- Associated Translocations

Genomic rearrangement through chromosome translocation is the most common mechanism for gene activation. Such translocation can lead to overexpression of a gene with critical function through fusion with a strong promoter or enhancer, or to create a chimeric protein with a constitutive activation of a cytokine receptor or a kinase. In Ph-like ALL, the ABL activating lesions are all fusion genes. There are various *ABL1* and *ABL2* fusions leading to constitutive activation of ABL class kinase [6, 7]. Two recurrent fusions leading to constitutive activation of cytokine receptors have also been reported in Ph-like ALL. One is *EBF1-PDGFRB*, a fusion of early B-cell factor 1 (*EBF1*) and platelet-derived growth factor receptor beta (*PDGFRB*) [6, 7], resulting in the loss of a B-cell differentiation factor and constitutive activation of tyrosine kinase *PDGFRB*. The other is *CSF1R-SSBP2*, a fusion of colony stimulating factor 1 receptor (*CSF1R*) and a single strand DNA binding protein 2 (*SSBP2*), involved in the regulation of genomic stability and also a fusion partner of *JAK2* [10].

Recurrent fusions involving the JAK signaling include CRLF2 and PAX5. About half of the Ph-like ALL are characterized by abnormal expression of *CRLF2*, which is caused by either translocation into the immunoglobulin locus IGH or by fusion with the upstream promoter of a constitutive expressed gene *P2RY8*. This expression is often associated with additional activating mutations in *CRLF2*, *IL7R*, *JAK1*, or *JAK2* [6, 7]. JAK2 has many different fusion partners, with JAK2 kinase domain retained and constitutively activated in all the fusions. *PAX5-JAK2* fusion is recurrent, leading to loss of differentiation factor PAX5 with activation of JAK2 [11]. Examples of reported fusions resulted from ABL class- and JAK2 pathway-associated translocations are summarized in Table 1.

IKZF1 Deletion

Deletion of *IKZF1* gene in chromosome 7p has been detected in a substantial proportion of patients with Ph-like ALL, predominantly in patients without other common recurrent cytogenetic abnormalities [12]. *IKZF1* encodes transcription factor Ikaros, with essential roles in regulating lymphoid differentiation [13]. Significantly, deletion of *IKZF1* has been identified as a predictor of a poor prognosis, associated with an increased risk of relapse and decreased

Table 1: Examples of kinase rearrangements and potential targets in *BCR-ABL1*-like ALL

	3′ Gene	5′ Gene	Translocation	Tyrosine Kinase Inhibitor
ABL class rearrangements	*ABL1*	*ETV6*	t(9;12)	Dasatinib
	ABL1	*NUP214*	t(9;9)	Dasatinib
	ABL1	*RCSD1*	t(1;9)	Dasatinib
	ABL1	*RANBP2*	t(2;9)	Dasatinib
	ABL1	*SNX2*	t(5;9)	Dasatinib
	ABL1	*ZMIZ1*	t(9;10)	Dasatinib
	ABL2	*PAG1*	t(1;8)	Dasatinib
	ABL2	*RCSD1*	t(1;1)	Dasatinib
	ABL2	*ZC3HAV1*	t(1;7)	Dasatinib
	CSF1R	*SSBP2*	t(5;5)	Dasatinib
	PDGFRB	*EBF1*	t(5;5)	Dasatinib
	PDGFRB	*SSBP2*	t(5;5)	Dasatinib
	PDGFRB	*TNIP1*	t(5;5)	Dasatinib
	PDGFRB	*ZEB2*	t(2;5)	Dasatinib
JAK2 or EPOR rearrangements	*JAK2*	*ATF7IP*	t(9;12)	JAK2 inhibitor
	JAK2	*BCR*	t(9;22)	JAK2 inhibitor
	JAK2	*EBF1*	t(5;9)	JAK2 inhibitor
	JAK2	*ETV6*	t(9;12)	JAK2 inhibitor
	JAK2	*PAX5*	t(9;9)	JAK2 inhibitor
	JAK2	*PPFIBP1*	t(9;12)	JAK2 inhibitor
	JAK2	*SSBP2*	t(5;9)	JAK2 inhibitor
	JAK2	*STRN3*	t(9;14)	JAK2 inhibitor
	JAK2	*TERF2*	t(9;16)	JAK2 inhibitor
	JAK2	*TPR*	t(1;9)	JAK2 inhibitor
	EPOR	*IGH*	t(14;19)	JAK2 inhibitor
	EPOR	*IGK*	t(2;19)	JAK2 inhibitor
CRLF2 rearrangements	*CRLF2*	*IGH*	t(X/Y;14)	JAK2 inhibitor
	CRLF2	*P2RY8*	t(X/Y;X)	JAK2 inhibitor
Other rearrangements	*NTRK3*	*ETV6*	t(12;15)	Crizotinib
	PTK2B	*KDM6A*	t(X;8)	FAK inhibitor
	TYK2	*MYB*	t(6;19)	TYK2 inhibitor

Note: Each listed fusion product preserves the kinase domain as its 3′ fusion partner. The tyrosine kinase inhibitors are known or predicted to target the listed kinase in experimental models. Data are based on Reference [7].

event-free survival in pediatric B-ALL [12, 14, 15]. In addition, deletion of *IKZF1* is also a frequent event in *BCR-ABL1*-positive ALL and also seen at the progression of chronic myeloid leukemia to lymphoid blast crisis [16].

Mechanistically, experimental evidence has suggested that loss of Ikaros activity arrests precursor B-cells in the adherent, self-renewing, pro-proliferative phase and promotes their transformation to a malignant state [17, 18]. Moreover, the study by Joshi *et al.* [17] has indicated a therapeutic approach for Ikaros-deleted leukemia, through inhibition of integrin signaling by focal adhesion kinase (FAK) inhibitors.

Targeted Treatment

Ph-like ALL is characterized by a gene-expression profile similar to that of *BCR-ABL1*-positive ALL and is associated with a poor prognosis. Discovery of

genetic alterations involving ABL or JAK kinases in Ph-like ALL has offered targeted treatment opportunities with tyrosine kinase inhibitors going beyond *BCR-ABL1*-positive leukemia. Extensive preclinical studies have shown that activation of signaling pathways induced by specific translocations is sensitive to tyrosine kinase inhibitors. Successful responses of chemotherapy-refractory Ph-like ALL to tyrosine kinase inhibitor therapy have also been reported [7, 19, 20]. Clinical trials combining kinase inhibitors with chemotherapy hold promise to further improving the treatment of Ph-like ALL. An ongoing Phase 2 clinical trial sponsored by M.D. Anderson Cancer Center compares the combination of Ruxolitinib (JAK1/JAK2 kinase inhibitor) or Dasatinib (ABL-kinase inhibitor) with chemotherapy in Ph-like ALL patients [21].

Acknowledgements

The authors declare no conflict of interests.
Received: February 3, 2016 **Accepted**: February 19, 2016
Published: March 1, 2016

References

1. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114:937-951.
2. Zhao XF, Gojo I, York T, Ning Y, Baer MR. Diagnosis of biphenotypic acute leukemia: a paradigmatic approach. Int J Clin Exp Pathol. 2009;3:75-86.
3. Harrison CJ, Haas O, Harbott J, et al. Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfurt-Munster study group. Br J Haematol. 2010;151:132-142.
4. Mullighan CG. The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014;2014:174-180.
5. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol. 2009;10:125-134.
6. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012;22:153-166.
7. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014;371:1005-1015.
8. Izraeli S. Beyond Philadelphia: 'Ph-like' B cell precursor acute lymphoblastic leukemias - diagnostic challenges and therapeutic promises. Curr Opin Hematol. 2014;21:289-296.
9. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med. 2015;373:1541-1542.
10. Poitras JL, Dal Cin P, Aster JC, Deangelo DJ, Morton CC. Novel SSBP2-JAK2 fusion gene resulting from a t(5;9)(q14.1;p24.1) in pre-B acute lymphocytic leukemia. Genes Chromosomes Cancer. 2008;47:884-889.
11. Nebral K, Denk D, Attarbaschi A, et al. Incidence and diversity of PAX5 fusion genes in childhood acute lymphoblastic leukemia. Leukemia. 2009;23:134-143.
12. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009;360:470-480.
13. Olsson L, Johansson B. Ikaros and leukaemia. Br J Haematol. 2015;169:479-491.
14. van der Veer A, Waanders E, Pieters R, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood. 2013;122:2622-2629.
15. Boer JM, van der Veer A, Rizopoulos D, et al. Prognostic value of rare IKZF1 deletion in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. Leukemia. 2016;30:32-38.
16. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008;453:110-114.
17. Joshi I, Yoshida T, Jena N, et al. Loss of Ikaros DNA-binding function confers integrin-dependent survival on pre-B cells and progression to acute lymphoblastic leukemia. Nat Immunol. 2014;15:294-304.

18. Schwickert TA, Tagoh H, Gultekin S, et al. Stage-specific control of early B cell development by the transcription factor Ikaros. Nat Immunol. 2014;15:283-293.
19. Weston BW, Hayden MA, Roberts KG, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. J Clin Oncol. 2013;31:e413-416.
20. Lengline E, Beldjord K, Dombret H, Soulier J, Boissel N, Clappier E. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with EBF1-PDGFRB fusion. Haematologica. 2013;98:e146-148.
21. ClinicalTrials.gov [Internet] A service of the U.S. National Institutes of Health - [cited February 3, 2016]; Available from: https://clinicaltrials.gov/