

# OVERVIEW AND DIAGNOSTIC PROCESS

## *BCR-ABL1*-LIKE B-LYMPHOBLASTIC LEUKEMIA/LYMPHOMA SCREENING ASSAY

*BCR-ABL1*-like B-lymphoblastic leukemia/lymphoma (B-ALL) (or “Ph-like” ALL) is a neoplastic proliferation of lymphoblasts that has a gene expression profile similar to that of B-ALL with t(9;22)(q34.1;q11.2) *BCR-ABL1*, but lacks the disease-defining Philadelphia chromosome. The revised 4th edition of the WHO has included this disease as a provisional entity.<sup>1</sup> Here, we provide an overview of the genetic profile and clinical features of *BCR-ABL1*-like B-ALL and review how we diagnose these cases in a comprehensive and cost-effective way.

### WHAT IS *BCR-ABL1*-LIKE B-ALL?

Unlike other B-ALLs with recurrent genetic abnormalities, there is not a single, discrete cytogenetic or molecular abnormality that defines *BCR-ABL1*-like B-ALL. To date, there have been more than 60 different rearrangements and gene mutations associated with this entity. However, all of these changes give rise to a characteristic gene expression profile, which has been used in Children’s Oncology Group (COG) and adult trials to screen for *BCR-ABL1*-like B-ALL. Identifying these cases is important because the majority of mutations converge on pathways that are potentially amenable to the addition of tyrosine kinase inhibitors (TKIs), including *ABL*-class and JAK/STAT pathway inhibitors such as dasatinib or ruxolitinib, to conventional chemotherapy.<sup>2,3</sup>

### WHAT ARE THE MOST COMMON GENETIC ABNORMALITIES IN *BCR-ABL1*-LIKE B-ALL?

The most common abnormalities include *CRLF2* rearrangements, *JAK* mutations, and erythropoietin receptor (*EPOR*) rearrangements. All three of these categories lead to activation of the JAK/STAT pathway. Mutations involving *ABL*-class genes include *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*. Other mutations and fusions include *IKZF1*, *FGFR1*, and *RAS*.<sup>2,4,5,6</sup>

### WHAT ARE THE CLINICAL FINDINGS IN PATIENTS WITH *BCR-ABL1*-LIKE B-ALL?

Comprehensive genomic profiling of *BCR-ABL1*-like B-ALL has been primarily performed in children enrolled in COG trials. Studies have demonstrated that *BCR-ABL1*-like B-ALL is associated with a poor prognosis and higher risk clinical features: Increased age, elevated white blood cell count at diagnosis, and a higher rate of end-of induction minimal residual disease.<sup>5</sup> The incidence increases across the age spectrum, occurring in approximately 10-20% of childhood cases of B-ALL and reaching 20-30% in adults. Among children, *BCR-ABL1*-like ALL is seen primarily among NCI high risk patients, although the rare NCI standard risk patients have inferior event-free survival compared to their non-*BCR-ABL1*-like counterparts.<sup>5,6</sup> Adults with *BCR-ABL1*-like B-ALL have significantly worse overall and event-free survival, with a 5-year survival of approximately 23%.<sup>7,8</sup>

### WHAT POTENTIAL THERAPEUTIC OPTIONS ARE AVAILABLE FOR THESE PATIENTS?

A number of TKIs are available, based on the type of mutation identified. For example, those involved in the JAK/STAT pathway may be responsive to the addition of ruxolitinib to conventional chemotherapy, while those with mutations involving the *ABL*-class genes may benefit from the addition of dasatinib or imatinib.<sup>2,3</sup> A number of clinical trials are currently underway evaluating the efficacy of the addition of TKIs to chemotherapy regimens in both newly diagnosed and relapsed patients. Other potential therapies may include FLT3-inhibitors, TRK inhibitors, and those targeting the RAS/MAPK signaling pathway.<sup>4</sup>

### WHICH PATIENTS SHOULD BE TESTED FOR *BCR-ABL1*-LIKE B-ALL?

*BCR-ABL1*-like B-ALLs have a poor prognosis, but may harbor mutations that may be responsive to the addition of a TKI combined with conventional chemotherapy. Therefore, screening should be performed in all children diagnosed with B-ALL who fall into the high risk category. The presence of t(9;22)(q34.1;q11.2) *BCR-ABL1* and t(12;21)(p13.2;q22.1) *ETV6-RUNX1* excludes the diagnosis of *BCR-ABL1*-like B-ALL and these patients do not need to be screened.<sup>5,6</sup> Since only a small subset of children with standard risk B-ALL harbor a targetable mutation, screening should be considered in this population if clinically indicated – this may be in cases in which there is residual disease at end of induction or if there is CNS or testicular involvement. Given that *BCR-ABL1*-like B-ALL accounts for 20-30% of adults diagnosed with B-ALL, adults should also be screened. These recommendations are in agreement with current NCCN Guidelines, which encourage assessment for *BCR-ABL1*-like gene fusions and mutations in cases negative for the Philadelphia chromosome.

### HOW IS *BCR-ABL1*-LIKE B-ALL DIAGNOSED?

Because of the spectrum of genetic abnormalities associated with the disease, several methods and approaches to diagnosing *BCR-ABL1*-like B-ALL have been described. Gene expression profiling remains the gold standard.<sup>9</sup> COG and adult trials have utilized a low density array (LDA) card assay to quickly and efficiently screen cases for the characteristic gene expression signature. In positive cases, additional work up to identify the specific mutation is then performed.<sup>5,6</sup> TriCore Reference Laboratories offers this same simple and comprehensive approach, starting with screening using the LDA assay (see algorithm). We then reflex as necessary to additional assays including FISH rearrangements in high-incidence genes, a RNA gene fusion panel, and a multiplex next generation sequencing panel evaluating a large number of genes known to be associated with *BCR-ABL1*-like B-ALL.<sup>5,6,10</sup> We believe this approach is unique in being both cost-effective and comprehensive. Alternatively, flow cytometry for surface *CRLF2* expression could be considered but is not always associated with a rearrangement. Whole exome, transcriptome, and genome sequencing have also been performed with varying results and may be limited due to availability, time, and cost.<sup>10</sup>

### SUMMARY

*BCR-ABL1*-like B-ALL has a similar gene expression profile to that of *BCR-ABL1* B-ALL, but without the presence of the t(9;22) (q34.1;q11.2) Philadelphia chromosome. It is associated with poor prognosis and is seen in 10-20% of pediatric cases and 20-30% of adult cases. A variety of different genetic abnormalities are identified in this entity, but they all converge on pathways that are potentially responsive to the addition of targeted therapy to conventional chemotherapy. Thus, it is important to screen for *BCR-ABL1*-like B-ALL, particularly in adults and pediatric patients with high-risk clinical features. A stepwise algorithmic approach to diagnosis provides comprehensive evaluation while saving costs by only performing those assays that are necessary for each particular patient.

### CONTACT

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### REFERENCES

1. Borowitz MJ, Chan JKC, Downing JR, et al. B-lymphoblastic leukemia/lymphoma with recurrent cytogenetic abnormalities. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC; 2017:208.
2. 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(11):1005-15.
3. *Haematol*. 2017;30(3):222-228.
4. Tasian SK, Loh ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. *Blood*. 2017;130(19):2064-2072.
5. Reshmi SC, Harvey RC, Roberts KG, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. *Blood*. 2017;129(25):3352-3361.
6. Roberts KG, Reshmi SC, Harvey RC, 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; epub ahead of print.
7. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood*. 2017;129(5):572-581.
8. Roberts KG, Gu Z, Payne-turner D, et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. *J Clin Oncol*. 2017;35(4):394-401.
9. Harvey RC, Kang HN, Roberts KG, 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 [abstract]. *Blood*. 2013;122:826.
10. Siegele BJ, Nardi V. Laboratory testing in BCR-ABL1-like (Philadelphia-like) B-lymphoblastic leukemia/lymphoma. *Am J Hematol*. 2018;93(7):971-977.