Letters: Ph-like ALL

November 2018—In the October issue of CAP TODAY, Karen Titus shared with us a story titled, “Fresh incentive to look for Ph-like ALL.” She spoke with key players in the discovery of *BCR-ABL1*-like B-lymphoblastic leukemia/lymphoma (B-ALL) (or “Ph-like” ALL), which is now a provisional entity in the 2016 revised fourth edition of the WHO. A key takeaway from the article is that Ph-like ALL is a genetically heterogeneous disease with more than 60 different rearrangements and mutations identified to date, and more being discovered. This is unlike any other ALL subtype, which has a specific, recurrent genetic alteration. However, the unifying finding is a common gene expression signature, one that manifests as a result of alterations in genes that activate kinase and cytokine receptor signaling. It is these alterations that may be amenable to targeted therapies such as JAK2 inhibitors and tyrosine kinase inhibitors. Which targeted therapy, however, depends on the specific mutation identified in each particular case.

Given the diversity of mutations in Ph-like ALL, the approach to diagnosing this entity can be quite complex. Titus’ article discusses the development of a “clinical diagnostic assay used for screening,” which has been FDA approved for clinical trials. This screening test is a low-density array (LDA) assay, used to evaluate for the common gene expression signature identified in Ph-like ALL. This same LDA assay is now commercially available from TriCore Reference Laboratories. We have optimized and validated the assay in conjunction with Dr. Willman’s laboratory at the University of New Mexico, the same individuals who first identified and characterized this disease.

Furthermore, TriCore offers a comprehensive diagnostic algorithm to characterize the genomic profile of each individual’s case of ALL, if it turns out to harbor the Ph-like signature. In our algorithm, we screen for Ph-like ALL using the LDA assay by evaluating both the eight-gene and 15-gene signatures. If the LDA screen demonstrates that a particular case does have the Ph-like signature, the next step would be to identify the specific mutation present to guide targeted therapy. Additional studies may include FISH and other molecular studies, if deemed appropriate. With this approach, TriCore offers Ph-like ALL screening in a comprehensive yet cost-effective approach, performing only the testing necessary to make a diagnosis of Ph-like ALL and identify which genetic alteration is present. If the rearrangement or mutation is present within the JAK/STAT pathway, then a JAK inhibitor such as ruxolitinib may be considered. If the rearrangement or mutation is present with an *ABL*-class gene, then a tyrosine kinase inhibitor such as dasatinib or imatinib may be considered.

Ph-like ALL occurs in 15 to 20 percent of high-risk pediatric ALL and 20 to 30 percent of adult cases, potentially higher in Hispanic and Native American populations. It is relatively common, and given that the prognosis is generally poor, it is important to be able to identify patients who are Ph-like so they may benefit from clinical trials and targeted therapies. However, the comprehensive algorithm to identify genetic abnormalities can get expensive, depending on the number of additional tests required. Therefore, the judicious use of a sensitive yet specific screening assay is critical to identifying only the 15 to 30 percent of cases that need to be advanced for further testing. This is the advantage of TriCore’s LDA screening assay and algorithm—to properly triage cases that should and should not continue on for additional cytogenetic and molecular testing. Additionally, with the University of New Mexico’s hematopathologists and molecular genetic pathologists performing the testing and providing the interpretations, expert guidance will be provided through every step of the algorithm.

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