En-Abl-ing treatment of “Ph-like” ALL?

Tanasi, Ba and colleagues\(^1\) present a succinct yet thorough summary of 24 patients with ‘Ph-like ALL-associated alterations’. The report includes the diagnostic approaches, clinical responses, and overall outcomes of these patients. Given the paucity of information on this disorder, this report will be of particular value to practicing clinicians.

“Ph-like” or “BCR-ABL1-like” ALL is characterized by a diverse group of genetic alterations that activate cytokine receptor and kinase signaling, leading to a gene expression profile similar to that of BCR-ABL1 expressing ALL. Not surprisingly, these alterations result in a poor response to standard chemotherapy, with responses similar to those found in BCR-ABL1 expressing ALL. In 2009, “Ph-like” or “BCR-ABL1-like” ALL was independently described by the Children's Oncology Group (COG)/ St. Jude Children's Research Hospital\(^2\) and the Dutch Childhood Oncology Group\(^3\) using gene expression profiling. Despite these reports, there is still no single diagnostic test or universally agreed approach to uncovering this entity in clinical practice. The complexity of this diagnostic issue has recently been reviewed in detail by Kathryn Roberts\(^4\).

As a practical summary, the majority of patients with this entity will have either (1) JAK-STAT pathway abnormalities, most of which involve cytokine receptor-like factor-2 (CRLF2) signaling, through which the
JAK-STAT pathway is activated (for example *IGH-CRLF2, P2RY8-CRLF2* translocations), or other fusions activating that same pathway including but not limited to those affecting JAK2 and EPOR, the erythropoietin receptor or (2) ABL-class fusions, including *ABL1, ABL2, CSF1R, LYN* and *PDGFα/β* gene fusions. There are reports of cell lines and primary cells harboring ABL-class fusions responding to dasatinib⁵, but also, a recent clinical report of resistance to imatinib developing via a *PDGFRB*C843G mutation⁶.

Despite these scientific advances, there remains little information available to guide clinicians when faced with this entity in their patients. In this context, the short report of patients treated by the French GRAALL and FRAALLE groups illustrates the real-world outcome of a small group of patients with “Ph-like” ALL in the first category, namely those who have ABL-class fusions. The significance of this report is threefold. First, it clearly illustrates that, despite the potential for diagnostic complexity, many of the relevant genetic abnormalities can be detected by a relatively simple screening strategy directed at identifying known, targetable lesions using established cytogenetic and PCR techniques. These techniques are well within the capability and pocket of most modern diagnostic laboratories. Second, it illustrates how patients with this entity have presented in real life, helping early recognition of when it should be suspected clinically, where a pre-emptive diagnostic approach is not yet available. Seven of the cohort of 19 relatively young patients did not reach CR after intensive induction therapy and 11 of the 19 had a poor prednisolone response. Furthermore, among those who did reach CR, the majority still had high-level minimal residual disease. Hence, poor response to initial therapy should be a strong red-flag to immediately seek further diagnostic information to confirm or rule out “Ph-like” ALL. Third, some of these patients in this case series appeared to benefit from the introduction of TKI, further strengthening the need to make an early diagnosis and to urgently seek
alternative or additional therapeutic agents to conventional chemotherapy.

Clearly, this report is a retrospective series of cases. It does not inform us about incidence, and we cannot know the denominator, namely, if there are other patients with unidentified ABL-class fusions who had a successful outcome without TKI. It is important to note that the ongoing prospective trial AALL131 (NCT 02883049) from the COG will evaluate the outcome with the addition of dasatinib started after month 1 of therapy. Until the outcome from the COG trial is known, physicians who need published outcome data to be allowed to prescribe TKI therapy for ABL-class fusions will find the current data helpful.

Finally, whilst we are now clear that “Ph-like” ALL portends a poor response to conventional chemotherapy, we do not yet know the clinical and prognostic relevance of these lesions in the era of immunotherapy. It is incumbent on all ongoing immunotherapy trials to make stringent efforts to identify “Ph-like” ALL, and document subgroup analyses in their statistical plans. Whenever possible, material from completed immunotherapy studies should be evaluated retrospectively, to document the responses within this subtype of ALL.
References


