immunotherapeutic strategies. Therefore, the identification of surrogate biomarkers for tumor immunogenicity (eg, genomic complexity and mutational burden), host immunologic competence (eg, T-cell repertoire), and the tumor microenvironment (eg, expression of immunologic "checkpoints") may improve our ability to distinguish patients for whom ECP monotherapy is sufficient from those who may benefit from ECP in combination with other agents (see figure). However, at least for now, the findings reported by Gao et al are clear: in the course of SS/eMF treatment, ECP should take center stage early, enjoy the spotlight in the first act, be ushered off stage in the second, and rarely (if ever) be invited for an encore.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Tanasi et al, page 1351

En-Abl-ing treatment of "Ph-like" ALL?

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In this issue of *Blood*, Tanasi and colleagues[1] present a succinct yet thorough summary of 24 patients with "Ph-like acute lymphoblastic leukemia (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*-positive ALL. Not surprisingly, these alterations result in a poor response to standard chemotherapy, with response rates similar to those found in *BCR-ABL1*-positive 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 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 (eg, *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 dasatinib,[5] but also, a recent clinical report of resistance to imatinib developing via a $PDGFRB^{C843G}$ mutation.[6]

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 polymerase chain reaction 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 preemptive diagnostic approach is not yet available. Seven of the cohort of 19 relatively young patients did not reach complete remission

(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 tyrosine kinase inhibitor (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 (#NCT02883049) 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, although 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.

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