Philadelphia chromosome-like acute lymphoblastic leukemia. Still a pending matter

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New genetic abnormalities affecting risk assessment and patient stratification have been reported in B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) defining novel subtypes. Some of these subtypes have been included in the most recent World Health Organization classification.[1] Almost 10 years ago, two independent studies identified a subset of pediatric ALL characterized by a specific gene expression profile similar to that of Philadelphia (Ph) chromosome-positive ALL.[2,3] This novel ALL subtype, called Ph-like ALL or *BCR-ABL1*-like ALL, is a frequent ALL subtype that comprises up to 15% of pediatric BCP-ALL. Its incidence reaches 25% in adolescents and young adults and 20% in adults and it is generally recognized as being associated with a poor prognosis at any age[4]

Ph-like ALL is characterized by multiple genetic aberrations that converge on tyrosine kinase and cytokine receptor signaling pathways.[5] According to the signaling pathway involved several subgroups have been defined. These include *CRLF2* rearrangements or mutations, fusions involving *ABL*-class genes, *Ras* signaling pathways and other less common fusions. Alterations in the *CRLF2* gene are the most frequent and result in overexpression of this gene and an increase of CRLF2 protein expression. Aberrant *CRLF2* expression frequently co-occurs with *JAK* activating mutations or other mutations deregulating JAK/STAT signaling (*e.g.*, *IL7R* mutations). Deregulation of JAK/STAT signaling may also be due to *JAK2* or *EPOR* rearrangements or additional alterations activating other JAK/STAT signaling genes. In turn, the subgroup of *ABL*-class fusions involving *ABL1*, *ABL2*, *CSF1R* and *PDGFRB* accounts for 15-20% of Ph-like ALL cases.

Since kinase-activating alterations are frequent in Ph-like ALL and most converge on clinically actionable signaling, there is great interest in the early identification of Ph-like patients, with the aim of improving the prognosis with the use of tyrosine kinase inhibitors (TKI). However, identification of Ph-like ALL is currently challenging, and appropriate assays are not yet available for use as routine diagnostic approaches.[6]

In this issue of *Haematologica*, Chiaretti *et al.* screened 88 BCP-ALL cases negative for the major fusion genes (*BCR-ABL1*, *ETV6-RUNX1*, *TCF3-PBX1* and *KTM2A*) enrolled in the pediatric-inspired, measurable residual disease (MRD)-driven GIMEMA LAL1913 front-line protocol for adults with Ph-negative ALL in order to assess response to the treatment and prognosis.[7] Twenty-eight of these 88 cases (31.8%) showed the Ph-like phenotype. Screening for Ph-like ALL was performed successfully using the "BCR/ABL1-like predictor" developed by the GIMEMA Group.[8] This model is based on the identification of nine genes specifically overexpressed by adult Ph-like ALL cases and uses their expression values together with *CRLF2* transcript quantification by real time quantitative polymerase chain reaction to build this predictive tool. This study showed that Ph-like patients had a lower complete response rate, event-free survival and disease-

Table 1. Clinical trials either specific for Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL patients) or including patients with Ph-like ALL*.

NCT number	Group	Schedule	Phase	N patients planned or enrolled	Age (yrs)	Status
02883049	COG	Dasatinib Ruxolitinib	3	5,956	1-30	Active, not recruiting
02723994	COG	Ruxolitinib	2	170	1-21	Recruiting
03117751	SJCRH	Dasatinib Ruxolitinib	2/3	1,000	1-18	Recruiting
02420717	MDACC	Dasatinib Ruxolitinib	2	92	≥10	Active, not recruiting
03571321	University of Chicago	Ruxolitinib	1	15	18-39	Recruiting
03643276	AIEOP/BFM	Bortezomib Blinatumomab	3	5,000	≤17	Recruiting
02716233	Assistance Publique - Hôpitaux de Paris	Imatinib	3	1,578	1-18	Recruiting
03007147	COG EsPhALL	Imatinib	3	700	2-21	Recruiting
03564470	Nanfang Hospital Guangzhou	Chidamide Dasatinib	2	120	14-55	Unknown

*Clinicaltrials .gov. accessed on November 28, 2020. COG: Children's Oncology Group; SJCRH: Saint Jude Childrens Research Hospital; MDACC: MD Anderson Cancer Center; AIEOP: Associazione Italiana di Ematologia e Oncologia Pediatrica; BFM: Berlin-Frankfurt-Münster; EsPhALL: European PhALL Consortium; yrs: years.

free survival, as well as greater MRD persistence when treated with a pediatric-oriented and MRD-driven adult ALL protocol, thus reinforcing the contention that early recognition of Ph-like ALL is crucial to refine risk-stratification and optimize therapeutic strategies. While some conflicting results on the prognosis of Ph-like ALL have been reported in pediatric patients, the results of this study are concordant with those of other studies performed in adults, uniformly showing a poor prognosis for this ALL subtype.[4,9,10] An important finding of this study is the correlation between the Ph-like phenotype and the poor MRD clearance at all the time points analyzed, but especially at week 10 of the protocol, a time point used for the decision to proceed or not to hematopoietic stem cell transplantation (HSCT) in this trial. In fact, the Ph-like profile proved to be the only risk factor for MRD positivity at this time point. This finding is relevant since half of the patients were considered *a priori* as standard risk according to their features at baseline. In addition, Ph-like ALL patients from this trial showed inferior cytologic complete response after induction therapy (a feature not shown in all studies)[11] indicating that better induction therapies are needed for these patients. This study also suggests that HSCT is beneficial in these cases and should be pursued at the earliest opportunity in order to increase event-free survival.

It seems clear that apart from early recognition, the management of Ph-like ALL patients should be optimized, and many efforts are currently addressed to improve the results of therapy. These efforts are mainly focused on the incorporation of targeted therapies and immunotherapy to the chemotherapy schedules. TKI inhibitors (*e.g.*, imatinib, dasatinib and ruxolitinib), histone deacetylase inhibitors (*e.g.*, chidamide) and bispecific monoclonal antibodies (*e.g.*, blinatumomab) are the compounds most frequently evaluated in clinical trials (Table 1). However, there is scarce information available on the results of these approaches. As an example, a recent retrospective report by Tanasi *et al.* showed that the introduction of TKI frontline during consolidation improved MRD-negative status and was associated with a 3-year OS of 77% in a small series of 24 adult patients.[12]

Clinical trials are limited in Ph-like ALL. Regarding pediatric trials, in the ongoing trials of the Children's Oncology Group (COG) (clinicaltrials gov. Identifier: NCT028830499 and in the Total Therapy XVII trial of the Saint Jude Children's Research Hospital [SJCRH] clinicaltrials gov. Identifier: NCT03117751),[13] patients with National Cancer Institute (NCI) high-risk characteristics or poor early MRD response, who are positive for *ABL* class fusions and *JAK* pathway mutations, receive dasatinib and ruxolitinib, respectively, together with conventional frontline chemotherapy from consolidation until the end of maintenance therapy. The COG ALL1521 trial (clinicaltrials gov. Identifier: NCT02723994) is investigating the benefit of adding ruxolitinib to backbone COG based NCI high-risk chemotherapy for patients with CRLF2-rearranged ALL. In the study by the European ALLTogether consortium, patients with *ABL*-class fusions at diagnosis receive TKI on top of chemotherapy from day 15 of induction; HSCT is indicated in cases with poor MRD response. In the French CALL-F01 protocol (clinicaltrials gov. Identifier: NCT02716233), RNA sequencing is performed in all B-other ALL in case of induction failure or MRD positivity. Imatinib is given in combination with chemotherapy in the high-risk group, and HSCT is indicated in poor responders. The early introduction of TKI in addition to chemotherapy in *ABL*-class positive BCP-ALL is planned to be evaluated within an intercontinental collaborative trial (clinicaltrials gov. Identifier: NCT03007147) involving the COG and EsPhALL (European PhALL Consortium) groups.

Clinical trials for AYA and adult patients are even more limited. Phase I/II trials conducted at the MD Anderson Cancer Center are testing dasatinib or low doses of ruxolitinib in combination with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) in relapsed/refractory ALL and *ABL*-class fusions or *CRLF2/JAK* mutations, respectively. Interim data analysis has demonstrated the safety of these combinations with limited efficacy.[9] A recent phase I trial at the University of Chicago and other institutions is studying ruxolitinib in combination with the pediatric-inspired CALBG (Cancer and Acute Leukemia Group B) 10403 chemotherapy regimen in adolescents with newly diagnosed Ph-like ALL harboring *CRLF2/JAK* alterations, with a planned phase II expansion study if safety is demonstrated.

Regarding the election of TKI, there is no clear evidence of the superiority of dasatinib over imatinib for Ph-like ALL cases with *ABL*-class fusions. This comparison is especially difficult given that the doses of these TKI differ among trials. Other TKI, such as nilotinib, bosutinib and ponatinib, are still being investigated as phase I and II trials in pediatric cancers. Since the combination of TKI and immunotherapy with blinatumomab has proven feasible and effective in patients with Ph-positive ALL,[14] this approach should be explored in patients with Ph-like ALL together with reduced-intensity chemotherapy and HSCT.[15,16]

There are challenges in the diagnosis of Ph-like ALL before using targeted therapy in frontline treatment. Diagnostic technologies such as RNA sequencing and similar strategies should be implemented in a timely fashion for all "B-other ALL", but to date appropriate assays are not yet available as widely recognized diagnostic approaches.[17-19] Furthermore, although *ABL*-class and *JAK*-pathway alterations account for most Ph-like ALL cases, there are also several alterations involving kinases that are not inhibited by either TKI or JAK inhibitors. For this subgroup of Ph-like cases without known targetable lesions innovative therapies such as immunotherapy could be useful to reduce the MRD level before MRD-guided HSCT.[20] Nonetheless, all these efforts will undoubtedly require collaborative international approaches to conduct successful studies.

Disclosures

No conflicts of interest to disclose.

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Granulocyte colony-stimulating factor acts on lymphoid-biased, short-term hematopoietic stem cells

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Granulocyte colony-stimulating factor (G-CSF) is a cytokine that increases myelopoiesis,[1] impairs lymphopoiesis by inhibiting committed progenitor cells,[2,3] and enhances hematopoietic stem cell (HSC) mobilization.[4] The direct effects of G-CSF on purified subpopulation of HSC remained to be delineated. In this issue of *Haematologica*, Xie *et al.*[5] investigate the influence of G-CSF on proliferation and the repopulating potential of myeloid-biased, long-term HSC ($CD201^+CD150^+CD48^-CD41^-CD34^-$KSL) and lymphoid-biased, short-term HSC ($CD201^+CD150^-CD48^-CD41^-CD34^-$KSL).

Understanding the direct influences of G-CSF on HSC could improve our understanding of HSC responses to an increase in G-CSF level caused by inflammation.[6] The study by Xie *et al.* shows that G-CSF acts directly on lymphoid-biased, short-term HSC but not on myeloid-biased HSC. Interestingly, G-CSF cooperates with stem cell factor in driving the expansion of lymphoid-biased, short-term HSC in culture and in maintaining the *in vivo* repopulating potential of such cultures. These findings suggest that G-CSF-mediated effects on lymphoid-biased, short-term HSC may contribute to the previously noted enhancement of early lymphopoiesis of bone marrow stem and progenitor cells after exposure to G-CSF.[7] In contrast, however, G-CSF is also known to instruct bone marrow stromal cells to suppress the function of committed progenitors of B-lymphopoiesis.[2] The functional relevance of the G-CSF-mediated priming of early lymphoid progenitor cells and lymphoid-biased HSC[5,7] in association with G-CSF-mediated impairment in the progression of lymphopoiesis from committed progenitor cells[2] should be delineated in future studies.

The primary role of G-CSF is currently seen in activation of myelopoiesis to strengthen myeloid immune responses, such as the recruitment of neutrophils during bacterial lung infections.[8] However, the simultaneous priming of early lymphoid progenitor cells and lymphoid-biased HSC by G-CSF may also be important to ensure prompt reactivation of lymphopoiesis after the initial induction of myeloid cell-driven immune responses. The sequential coordination of such immune actions by G-CSF seems to be an interesting area of future research.

Understanding direct influences of G-CSF on HSC could also be relevant for our understanding of HSC