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BCR-ABL1-like acute lymphoblastic leukemia in childhood and targeted therapy

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Acute lymphoblastic leukemia (ALL) is a constellation of diseases driven by genetic alterations commonly derived from structural chromosome rearrangements, aneuploidy and co-operating mutations in genes that encode for transcription factors regulating lymphoid development, tumor suppressors, proteins regulating cell cycle progression, and epigenetic modifiers.[1]

Recent years have witnessed dramatic progress in ALL classification. Subtypes of ALL can be defined according to the nature of specific sentinel genetic aberrations that confer distinct biological and clinical characteristics. Some of them represent a therapeutic target for specific treatments, which may contribute to a further increase in cure rates, to reduce the intensity of conventional chemotherapy and/or the need for hematopoietic stem cell transplantation (HSCT).

One of the first genetic aberrations identified was the Philadelphia chromosome (Ph), characterized by the t(9;22)(q34;q11) translocation that produces the *BCR-ABL1* gene, and, in turn, a constitutively active tyrosine kinase. *BCR-ABL1* fusion is present in 3-5% of pediatric ALL and in 25% of adult ALL patients. The evidence of this genetic aberration allowed the introduction of targeted therapy with tyrosine kinase inhibitors (TKI), which has dramatically improved the outcome of this subset of ALL.[2-10] The pediatric COG AALL1131 and AALL0622 studies, and the contemporary EsPhALL2004 and subsequent EsPhALL2010 trials, in fact, showed a clear advantage in Ph positive (Ph$^+$) ALL from early, continuous and protracted exposure to TKI combined with chemotherapy, challenging the indications for HSCT.[5-10] Of note, however, the combination of chemotherapy and TKI may also be associated with increased toxicity, as shown in the EsPhALL2010 study.[6,7]

With advanced technologies, such as whole genome and transcriptome sequencing, novel genetic subtypes have recently been discovered. In 2009, among the so called "B-other", a subgroup of B-cell precursor (BCP)-ALL lacking the known sentinel BCP-ALL genetic aberrations, a new category of ALL has been described by Mullighan[11] and by den Boer[12], and termed Philadelphia chromosome (Ph)-like and *BCR-ABL1*-like ALL, respectively. The second term is used in this paper. The two signatures are based on the prediction analysis of microarrays (PAM) classifier consisting of 257 gene probe sets trained on Ph$^+$ ALL cases (Mullighan[11]) or on hierarchical clustering of 110 gene probe sets identified to predict the major pediatric ALL subtypes (den Boer), with only nine overlapping probe sets.[12] *BCR-ABL1*-like ALL, defined by a gene expression profile greatly similar to that of Ph$^+$ ALL, presents a high frequency of deletions of *IKZF1*, which encodes the lymphoid transcription factor IKAROS, and of other lymphoid transcription factor genes.[11,13] *BCR-ABL1*–like ALL has been recognized as a provisional entity in the 2016 World Health Organization classification of myeloid neoplasms and acute leukemia;[14] the prevalence varies with age from 12% in children to 21% in adolescents, 27% in young adults, and 20-24% in older adults with BCP-ALL. In addition to older age at diagnosis, *BCR-ABL1*–like ALL is associated with other high-risk clinical features, such as elevated leukocyte count at diagnosis and poor treatment response, i.e. high levels of end-induction minimal residual disease (MRD), increased risk of induction failure and of relapse.[11,13,15-30]

Importantly, *BCR-ABL1*-like ALL is not defined by a single unifying sentinel molecular aberration; but rather, it is characterized by a variety of genomic alterations that activate kinases and deregulate cytokine receptor signaling. Fusion genes involving at least 17 cytokine receptors or tyrosine kinases have been identified.[23,29,31,32] These alterations can be grouped into several major subclasses: approximately 50% of *BCR-*

ABL1-like cases harbor rearrangements of the cytokine receptor like factor 2 (CRLF2) resulting in upregulation of CRLF2 expression, in the vast majority as a consequence of either a translocation resulting in *IGH-CRLF2* juxtaposition or a deletion of the PAR region of the X chromosome leading to the *P2RY8-CRLF2* fusion. Frequent concomitant activating gene mutations occur in Janus kinases or other regulators of JAK-STAT signaling, with about 50% of CRLF2 rearranged cases presenting *JAK1* or *JAK2* point mutations.[15,16,33,34] However, although the *P2RY8-CRLF2* rearrangement is associated with an intermediate to poor outcome, its role with respect to relapse disposition is not fully clear, as the *P2RY8-CRLF2* rearrangement has been reported in some cases to be lost at relapse, particularly when it has been identified initially in a sub-clone only.[35-38] About one-third of *BCR-ABL1*-like non-CRLF2 rearranged ALL cases present chromosomal rearrangements that result in constitutive deregulation of a cytokine receptor or the formation of kinase fusion genes: a major subgroup includes ABL-class alterations involving *ABL1*, *ABL2*, *CSF1R*, *LYN*, *PDGFRA* and *PDFGRB*. A second major group regards rearrangements that activate JAK family kinases, including *JAK2*, *EPOR*, *TYK2* and *IL2RB*. A third group constitutes a variety of other kinases or cytokine receptor alterations such as *NTRK3*, *FLT3*, *FGFR1* and *BLNK*, and the RAS signaling pathway.[11,13,23, 29,32-39]

The limited data available confirm that *BCR-ABL1*-like ALL is associated with high-risk features also in pediatric patients. A single institution reported that the outcome in *BCR-ABL1*–like ALL patients, although inferior to that of other patients, was favorable with MRD-driven therapy and with the majority of patients treated in the higher risk arms and 15% undergoing HSCT.[23,24] Subsequently, the COG found that, within standard risk ALL patients defined by National Cancer Institute (NCI) criteria, Ph-like ALL patients had a still good, but significantly lower, event-free-survival and no significant difference in survival when compared to non-Ph-like NCI standard risk ALL.[40] In keeping with these data, Boer reported an increased cumulative incidence of relapse in *BCR-ABL1*–like ALL compared to non-*BCR-ABL1*–like B-other ALL.[26] Finally, the AIEOP-BFM study group has recently reported the outcome of ABL-class fusion positive BCP-ALL in a retrospective study, which, although limited by its retrospective nature, and especially by a potential selection bias towards cases with a poor treatment response, indicates that these patients have an overall poor prognosis.[41]

The role of CRLF2 abnormalities on *BCR-ABL1*-like ALL outcome is still controversial. The COG showed that, while high CRLF2-expression predicted a dismal outcome in high-risk patients, the two specific genomic CRLF2-lesions did not confer independent prognostic significance.[42] Similarly, CRLF2-rearrangements had no independent prognostic value in the Medical Research Council ALL97 trial,[43] while the AIEOP-BFM study group reported that *P2RY8-CRLF2* positive patients allocated in the non-HR group had a poorer prognosis.[35,36] However, it should be remembered that data on CRLF2-rearranged BCP-ALL are not exclusively restricted to cases with *BCR-ABL1*-like gene expression signature. Outcome data on *BCR-ABL1*-like ALL are summarized in Table 1. Overall, these data confirm that there is a clinical need for innovative targeted therapies which may be effective in this ALL subtype, as suggested by pre-clinical studies.

In vitro studies have, in fact, demonstrated constitutive activation of kinase signaling networks in subsets of *BCR-ABL1*–like ALL harboring JAK pathway aberrations,[42,44,45] and *in vivo* studies have demonstrated anti-leukemic activity of the type I JAK2 inhibitor ruxolitinib and of the dual PI3K/mTOR inhibitor gedatolisib given as a monotherapy in patient-derived xenograft models of JAK pathway–mutant *BCR-ABL1*-like ALL.[44,46-50] Other studies have reported superior anti-leukemic efficacy with the type II JAK inhibitor CHZ868, which synergizes with dexamethasone to induce apoptosis, suggesting that type II JAK2 inhibition may be more effective to target CRLF2-rearranged BCP-ALL. This may be because type II inhibitors stabilize JAK2 in the inactive conformation, and overcome the JAK2 hyperphosphorylation observed with type I JAK inhibitors which target the ATP binding pocket and stabilize JAK2 in the active conformation.[51] Likewise, pre-clinical experimental studies have shown that cell lines and human cells expressing ABL-class fusions, as well as patient-derived xenograft models, have marked sensitivity to the TKI such as imatinib and dasatinib, similarly to *BCR-ABL1* cells.[52]

Clinical studies are still very limited. A COG phase I trial (ADVL1011; *clinicaltrials.gov identifier: 01164163*) demonstrated the safety of JAK2 inhibitor ruxolitinib, given as monotherapy in children with relapsed or refractory cancers,[53] while anecdotal reports have provided evidence of efficacy of TKI (imatinib and dasatinib) to induce remission and clear MRD in patients with ABL-class fusions with poor response to previous chemotherapy.[54-56]

Optimal clinical management of pediatric *BCR-ABL1*-like ALL, thus, remains to be defined. The heterogeneous genomic landscape and the diverse array of targetable kinase-activating lesions of *BCR-ABL1*–like ALL require precise diagnostic strategies. Initially, the DCOG group used a validated Affymetrix gene expression array which included 110 probe sets, while the COG and SJCRH used an Affymetrix gene expression array with 255 probe sets to screen patients for *BCR-ABL1*-like ALL signature. Subsequently, COG first utilized a quantitative reverse transcriptase polymerase chain reaction (RT-PCR)-based low density array (LDA) platform to identify patients with *BCR-ABL1*-like ALL enrolled in their ALL COG front-line AALL1131 trial. As a second step, a series of multiplex RT-PCR assays, fluorescence *in situ* hybridization (FISH), and DNA sequencing to identify the underlying genomic aberration were applied.[57,58] The COG is now using Archer targeted RNA sequencing instead of multiplex RT-PCR assays. Alternatively, combined FISH or targeted RNA-next generation sequencing (NGS) strategies with probes capturing the recurrently fused genes can be successfully applied.[59] In the future, NGS-based whole transcriptome sequencing should allow the detection of all relevant gene fusions and mutations in one step, as recently demonstrated by Gu *et al.*[60] and Li *et al.*[61] This approach will facilitate the timed diagnosis and the early implementation of specific treatments. Of note, despite the large number of individual kinase alterations identified, the majority converge on a limited number of pathways that can be targeted.

The best therapeutic strategy for this subgroup of patients remains a matter of investigation. Several ongoing studies are assessing the role of the addition of TKI or ruxolitinib on top of chemotherapy in pediatric BCP-ALL harboring ABL-class fusions or CRLF2/JAK pathway alterations. In the current COG AALL1131 and AALL1521 (*clinicaltrials.gov identifier: 02883049 and 02723994*, respectively) and SJCRH Total Therapy XVII trials (*clinicaltrials.gov identi-*

Table 1. Outcome of *BCR-ABL1*-like acute lymphoblastic leukemia among different study groups.

Study group	Protocol	N. *BCR-ABL1(Ph)* - like ALL patients/total BCP-ALL	Outcome (CIR, EFS, OS)
Roberts *et al.*[23]	Total therapy XV, Total therapy XVI, P9906 AALL0232, E2993, C19802, C10102 and C10403	264/1725	5-years pEFS 58.2±5.3%, 41.0±7.4%, and 24.1±10.5% for children with high-risk ALL, adolescents, and young adults; 5-years pOS 72.8±4.8%, 65.8±7.1%, and 25.8±9.9% for children with high-risk ALL, adolescents, and young adults. Across all age groups OS rates were inferior to those among patients with non–Ph-like ALL (P<0.001 for both comparisons)
Roberts *et al.*[24]	Total therapy XV	40/344	5 -years pEFS 90.0% ± 4.7% *vs.* 88.4% ± 0.9%, P=0.41 in BCR-ABL1–like ALL *vs.* non-BCR-ABL1–like ALL; 5-years pOS 92.5% ± 4.2% *vs.* 95.1% ± 1.3%, P=0.41 in BCR-ABL1–like ALL *vs.* non-BCR-ABL1–like ALL
Roberts *et al.*[40]	COG AALL0331	206/1023 Standard-Risk ALL	7-years pEFS 82.4 ± 3.6% *vs.* 90.7 ± 1.0%, P=0.0022, Ph-like ALL *vs.* non–Ph-like ALL; 7-years pOS 93.2 ± 2.4% *vs.* 95.8 ± 0.7%, P=0.14, Ph-like ALL *vs.* non–Ph-like ALL
Boer *et al.*[26]	DCOG ALL-8, ALL-9, ALL10 COALL 06-97 and COALL 07-03	77/574	8-years pCIR 35% *vs.* 17%, P=0.07, BCR-ABL1–like ALL *vs.* non BCR-ABL1–like B-other ALL
Cario *et al.*[41]	AIEOP BFM ALL 2000 and AIEOP BFM ALL 2009	46 ABL-class fusion positive ALL	5-years pEFS was 49.1±8.9% , 5-years pOS 69.6±7.8% and 5-years CIR was 25.6±8.2%

ALL: acute lymphoblastic leukemia; BCP-ALL: B-cell precursor acute lymphoblastic leukemia; CIR: cumulative incidence of relapse; EFS: event-free survival; OS: overall survival.

fier: 03117751), ALL patients with NCI high-risk characteristics or poor early MRD response are screened for ABL-class fusions and JAK pathway mutations. In patients positive for these alterations, dasatinib and ruxolitinib, respectively, are given in combination with conventional front-line chemotherapy from the consolidation phase until the end of maintenance therapy.[57,62] Patients with NCI standard risk characteristics and early good MRD response are not included because available data on their outcome are very limited.[48,52] Other phase I/II trials conducted at the MD Anderson Cancer Center (*clinicaltrials.gov identifier: 02420717*) are testing dasatinib or low doses of ruxolitinib in combination with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) in adolescents and adults with relapsed/refractory ALL and ABL-class fusions or CRLF2/JAK mutations, respectively; interim data analysis demonstrates the safety of these combinations with limited efficacy.[63] A recent phase I trial (*clinicaltrials.gov identifier: 03571321*) at the University of Chicago and other institutions is studying ruxolitinib in combination with the pediatric-inspired CALBG 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.[64,65]

In Europe, the AIEOP-BFM ALL and ALLTogether study groups are also investigating the addition of innovative or targeted therapy on top of chemotherapy in *BCR-ABL1*-like ALL. In the AIEOP-BFM ALL 2017 trial (*clinicaltrials.gov identifier: 03643276*), patients are screened at diagnosis for *IKZF1* deletions, which are frequently found in *BCR-ABL1*-like ALL, and for additional deletions of genes relevant for B-cell development. Those cases defined as IKZF1 plus positive[66] with any MRD positivity after induction treatment are randomized to receive the proteasome inhibitor bortezomib in addition to chemotherapy during consolidation and to receive the bispecific T-cell engager (BiTE) antibody blinatumomab during post-consolidation treatment. Especially the approach to apply immunotherapy instead of extremely intensive high-risk blocks may be of advantage for ABL-class-fusion positive cases, bearing in mind the high rate of severe treatment-related complications in Ph^+ ALL patients treated with high-risk chemotherapy plus TKI. In the ALLTogether study, patients are screened for ABL-class fusions at diagnosis and those positive receive TKI on top of chemotherapy from day 15 of induction onward. In both AIEOP-BFM and ALLTogether studies, these patients have an indication for HSCT in case of poor MRD response. Likewise, the French CALL-F01 protocol (*clinicaltrials.gov identifier: 02716233*) has been amended in 2018 to bring to RNA sequencing all B-other ALL in case of induction failure or end of induction MRD above or equal to 10^{-3}: these patients are to receive imatinib on top of chemotherapy in the high-risk group. Then, according to subsequent MRD and effective exposure to imatinib, they either continue TKI plus chemotherapy or go to HSCT. A similar approach in the early introduction of a TKI in addition to chemotherapy in ABL-class positive BCP-ALL is planned within the EsPhALL2017/COGAALL1631 protocol (*clinicaltrials.gov identifier: 03007147*), the first intercontinental collaborative trial for the treatment of pediatric Ph^+ ALL involving COG and EsPhALL study groups. In this trial, an amendment is ongoing to extend the eligibility to patients with ABL-class fusion positive BCP-ALL and, thus, treat them with imatinib given early after diagnosis and continuously on top of high-risk chemotherapy.

Actually, in pediatric patients there is no clear evidence for superiority of a specific type of TKI. In the COG AALL0622 study, dasatinib (60 mg/m^2) was substituted for imatinib (340 mg/m^2) on top of the same chemotherapy backbone of the AALL0031 study with no benefit. The same dose of dasatinib was used also in a joint COG/EsPhALL study (BMS CA180372) on top of the EsPhALL therapeutic strategy with preliminary results which appear similar to the contemporary EsPhALL study

which used imatinib (300 mg/m^2). A very recent study, where dasatinib was used at a higher dose (80 mg/m^2) and randomized *versus* imatinib (300 mg/m^2), showed a superiority of dasatinib; however, follow up of this study was relatively short, and results in the cohort treated with imatinib were inferior to those obtained by the EsPhALL and COG groups with the use of imatinib, thus, challenging the evidence of superiority itself. Other TKI such as nilotinib, bosutinib and ponatinib are still being investigated as phase I and II trials in pediatric cancers. At this moment, the choice of both imatinib or dasatinib appears to be reasonable as TKI in frontline ALL protocols for children and adolescents.[7,9,10,67,68]

In summary, there are still some challenges to implanting targeted therapy into frontline ALL treatment. There is a need for an early identification of BCP-ALL harboring ABL-class and JAK-pathway alterations to allow prompt intervention with targeted therapy to reduce intensity of chemotherapy, and refine HSCT indications, as already shown for Ph$^+$ ALL.[5-10] Diagnostic technologies such as RNA sequencing and similar strategies should be implemented in a timely fashion for all "B-other ALL". Although ABL-class and JAK-pathway alterations account for most *BCR-ABL1*-like ALL cases, there are also several alterations involving kinases that are not inhibited by either TKI or JAK inhibitors. Future studies are required to assess the potential of targeted inhibitors of these kinases in model systems and human leukemic cells. In the meantime, for this subgroup of *BCR-ABL1*-like cases without known targetable lesions, the optimal treatment should be based on MRD response, and might include innovative therapies such as immunotherapy. Moreover, all ALL patients treated with targeted approaches should be registered and closely followed up on the molecular level as recently discussed by Elitzur and Izraeli in order to understand response and resistance to targeted treatment.[69] Due to the rarity of these clinical entities, collaborative international efforts are strongly needed to conduct successful studies.

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