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RESEARCH LETTER

Philadelphia chromosome-positive acute lymphoblastic leukaemia in children and adolescents: A changing treatment landscape and a methodological challenge

To the Editor,

Approximately 3%–5% of paediatric acute lymphoblastic leukaemia (ALL) is driven by the *BCR::ABL1* fusion gene resulting from t(9;22)(q34;q11.2), known as Philadelphia chromosome-positive (Ph+) ALL. As the treatment landscape of Ph+ ALL has rapidly shifted in the era of chemoimmunotherapy and tyrosine kinase inhibitors (TKIs), this perspective letter brings together experts to review treatment evolution of paediatric Ph+ ALL over the last two decades, highlight ongoing challenges and delineating future directions in optimizing therapy in successor paediatric Ph+ ALL trials.

As shown in large 'Ponte di Legno' intergroup retrospective studies, before TKIs, the 7-year event-free survival (EFS) and overall survival (OS) of Ph+ ALL children were ~30% and ~40%, respectively, with intensive multi-agent chemotherapy and haematopoietic stem cell transplantation (HSCT) in first complete remission (CR1) offered to all patients with a suitable donor (see references in Supplementary Material).[1] An addition of TKIs in subsequent trials led to rapid disease clearance and significant long-term survival improvement. Multiple studies conducted during the past two decades by the European intergroup study on Ph+ ALL (EsPhALL) and/or the Children's Oncology Group (COG) demonstrated significant improvements with 5-year EFS and OS of approximately 60% and 80%, respectively, with continuous TKI-based chemotherapy regimens (Table 1, see references in Supplementary Material).[2–6] Importantly, similar EFS and OS rates were observed across trials, regardless of TKI generation (imatinib or dasatinib) and chemotherapy backbone. This precision medicine paradigm also reduced treatment-related toxicity, via omission of prophylactic cranial irradiation for nearly all patients and substantial decrease of HSCT use in CR1. Overall, modern TKI-based therapies have transformed paediatric Ph+ ALL from the once-least favourable subtype of ALL into a more curable entity.

HSCT in CR1 for children with Ph+ ALL has diminished over the last 20 years from approximately 80% in the EsPhALL2004 trial[7] to <10% of patients in the most recent trials (reserved to patients with poor minimal residual disease (MRD) response after 10-week therapy, irrespective of 'high-risk' genetics such as *IKZF1*-plus, whose prognostic relevance remains unclear). The OS of paediatric Ph+ ALL also substantially improved from 40% in the pre-TKI era to 80% with TKI-containing regimens, highlighting post-relapse salvageability in the TKI era. Most patients with relapsed Ph+ ALL can now achieve the second complete remission (CR2) or beyond and proceed to HSCT consolidation (about 30% undergo HSCT in CR2); moreover, the high salvage rates reported in trials do not fully reflect the remarkable recent successes of modern B-cell antigen-targeted immunotherapies, such as blinatumomab, inotuzumab or chimeric antigen receptor T-cell therapies[8] (see references in Supplementary Material) which may ultimately improve OS rates further and/or reduce morbidity in post-relapse therapy. Indeed, the incorporation of blinatumomab plus TKI with minimal chemotherapy represents a major paradigm shift in the front-line treatment of adult Ph+ ALL, prompting investigation of analogous strategies in paediatrics. The newly opened international AALL2131/EsPhALL2022 (NCT 06124157, EU CT number 2025-520982-39-00) pilot study with continuous TKI replaces the traditional 8-week consolidation chemotherapy phase with two cycles of blinatumomab and intercalates a third blinatumomab block between subsequent chemotherapy courses (Supplementary Material). This pilot trial aims to establish new baseline outcomes of paediatric Ph+ ALL and to guide future therapeutic options.

Use of single-agent TKI 'maintenance' therapy in Ph+ ALL patients varies widely across the age spectrum. Most paediatric oncologists stop TKI at 2 years with completion of chemotherapy, although recent identification of the chronic myeloid leukaemia (CML)-like subtype raises the potential for prolonged TKI monotherapy maintenance, similar to approaches used in patients with chronic phase CML. Some paediatric oncologists also use TKI monotherapy after HSCT, for 1 or 2 years as clinically tolerated, although data regarding the potential of this approach in

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TABLE 1 Historical data in Ph+ ALL trials.

Ph+ ALL trial	Years (No. of pts)	Chemotherapy backbone	TKI	IT therapy CRT	CR1 HSCT	Cumulative incidence of death CCR	Cumulative incidence of relapse	EFS (95% CI)	OS (95% CI)
COG AALL0031 (cohort 5)[4]	2002–2006 (49)	AALL0031 (VHR COG)	Imatinib 340 mg/m^2	*Post-induction*: 18 IT All	41%	5 years: 10%	5 years: 21%	5 years: 69% (57%–83%)	5 years: 79% (68%–92%)
COG AALL0622[6]	2008–2012 (60)	AALL0031 (VHR COG)	Dasatinib 60 mg/m^2	*Post day 15 induction*: 18 IT CNS3 only	32%	5 years: 3%	5 years: 35%	5 years: 60% (46%–74%)	5 years: 86% (76%–96%)
EsPhALL2010[2]	2010–2014 (155)	HR BFM	Imatinib 300 mg/m^2	*Post IB*: 17 IT + 3 if CNS3 All	38%	5 years: 16%	5 years: 27%	5 years: 57% (49%–65%)	5 years: 72% (64%–79%)
CA180-372/ AALL1122[3]	2012–2014 (106)	HR BFM	Dasatinib 60 mg/m^2	*Post day 15 IA*: 17 IT CNS3 only	14%	5 years: 8.6%	5 years: 36%	5 years: 55% (45%–64%)	5 years: 82% (73%–88%)
CCCG-ALL-2015[5]	2015–2018 (92)	Modified Total XV-XVI	Dasatinib 80 mg/m^2	*Since diagnosis*: 19 IT None	1.1%	4 years: 5.6%	4 years: 20%	4 years: 71%[a] (56%–90%)	4 years: 88%[a] (81%–96%)
	vs.		vs.	vs.	vs.	vs.	vs.	vs.	vs.
	2015–2018 (97)	Modified Total XV-XVI	Imatinib 300 mg/m^2	*Since diagnosis*: 19 IT None	3.1%	4 years: 4.3%	4 years: 34%	4 years: 49%[a] (32%–75%)	4 years: 69%[a] (56%–86%)

Note: The 'IT therapy' column summarizes intrathecal therapy scheduled in the protocol (since enrolment specified in *italics*), either as MTX-IT or triple therapy (methotrexate/hydrocortisone/cytarabine).

Abbreviations: CCR, continuous complete remission; CI, confidence interval; CR1 HSCT, haematopoietic cell transplant in first complete remission; CRT, cranial radiotherapy; EFS, event-free survival; HR, high risk; IT, Intrathecal; OS, overall survival; TKI, tyrosine kinase inhibitor; VHR, very high risk.

[a]In the CCCG-ALL-2015 study, EFS and OS decreased of approximately 10% at 5 years (personal communication) and outcome for the imatinib arm was markedly inferior than that reported in other studies.

preventing relapse remain limited. In the adult setting, TKI discontinuation has not been standard clinical practice, although very recent data support the feasibility of stopping TKI in patients who did not undergo HSCT (see references in Supplementary Material).[9]

MRD in Ph+ ALL patients can be monitored using several techniques, including quantitative polymerase chain reaction (qPCR) assessment of *BCR::ABL1* fusion (at the transcript or DNA level), qPCR or, more recently, next-generation sequencing (NGS) analysis of immunoglobulin/T-cell receptor (IG/TR) rearrangements or flow cytometry (FC) immunophenotyping. In this context, detectable levels of MRD by any of these techniques may be interpreted by clinicians as signals of disease persistence or recurrence and thereby direct therapeutic interventions. Disease monitoring based on *BCR::ABL1* transcript levels is particularly controversial due to its high variability and unclear prognostic significance in paediatric Ph+ ALL. In some cases, *BCR::ABL1* qPCR may be frankly positive with concurrent negativity or very low positivity by other methods, consistent with a diagnosis of Ph+ ALL with multilineage involvement (or CML-like ALL) that has been identified in up to one-third of paediatric cases.[10] At the current time, it remains challenging to discriminate between primary Ph+ ALL versus CML in lymphoid blast crisis, particularly when the *BCR::ABL1* fusion gene encodes for the 210-kD protein (p210). In these cases, physicians may decide to protract TKI treatment because of persistent *BCR::ABL1* positivity, similar to the adult Ph+ ALL approach, although growth hindrance remains a relevant concern in paediatric patients.

Some experts recommend the monitoring of *BCR::ABL1* levels in peripheral blood every 3–6 months post-therapy to detect the early signs of molecular relapse and guide therapeutic decisions.[11] However, *BCR::ABL1* re-emergence in the absence of overt disease by other MRD assays can be a conundrum for treating physicians, who may opt for a watch-and-wait approach versus initiating TKI monotherapy or multidrug salvage therapy, despite such molecular findings not meeting traditional morphological or newer extended definitions of relapse.[12] Similar scenarios may exist when (possibly low) positivity of IG/TR PCR or FC MRD is redetected, suggesting impending relapse (representative case example in Table 2).

Notably, children with Ph+ ALL treated with front-line imatinib are more likely to receive dasatinib with second-line salvage chemotherapy upon relapse, even without evidence of emergence of resistance mutations. Newer TKIs (e.g. bosutinib, ponatinib, asciminib, olverembatinib) have also achieved high success in adults with relapsed/refractory Ph+ ALL and are under clinical investigation in children via early phase clinical trials (see references in Supplementary Material).[13]

TABLE 2 Extensive MRD monitoring of a patient diagnosed with Ph+ ALL at 13 years of age who was treated in Italy with chemotherapy and imatinib according to the EsPhALL2017/COGAALL1631 protocol for 2 years.

			IgH VH4 JH6			IgH VH1 JH6				*BCR::ABL1* RNA
	BM sample (month/year)	Protocol Phase	QR	SR	MRD	QR	SR	MRD	*BCR::ABL1* DNA	No. of copies/10000 *ABL* copies
End of October 2019: diagnosis of Ph+ ALL										
1	Nov 2019	d+15 induction	1×10^{-4}	1×10^{-5}	4.3×10^{-1}	1×10^{-4}	1×10^{-5}	6.4×10^{-1}	4.4×10^{-1}	na
2	Dec 2019	EOI	1×10^{-4}	1×10^{-5}	pos $<1\times10^{-4}$	1×10^{-4}	1×10^{-5}	neg	6.7×10^{-4}	3
3	Feb 2020	EOC	1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	pos $<1\times10^{-4}$	0.37
4	Jun 2022	1st year after stop therapy	1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	na	95
5	Jul 2022		1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	na	477
6	Sep 2022		1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	na	62
7	Nov 2022		5×10^{-4}	1×10^{-4}	neg	1×10^{-4}	1×10^{-5}	neg	na	105
8	Feb 2023	2nd year after stop therapy	5×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	na	33
9	Jun 2023		1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	na	227
10	Sep 2023		5×10^{-4}	1×10^{-4}	neg	5×10^{-4}	1×10^{-5}	neg	na	211
11	Dec 2023	3rd year after stop therapy	1×10^{-4}	1×10^{-4}	neg	5×10^{-4}	1×10^{-4}	pos $<5\times10^{-4}$	na	252
12	Jan 2024		5×10^{-4}	1×10^{-4}	neg	1×10^{-4}	1×10^{-4}	neg	1.1×10^{-2}	136
13	Jun 2024		1×10^{-4}	1×10^{-5}	pos $<1\times10^{-4}$	1×10^{-4}	1×10^{-4}	pos $<1\times10^{-4}$	4.6×10^{-3}	55
14	Sep 2024		5×10^{-4}	1×10^{-5}	1.2×10^{-3}	5×10^{-4}	1×10^{-5}	pos $<5\times10^{-4}$	8.0×10^{-3}	299
15	Oct 2024		5×10^{-4}	1×10^{-4}	4.7×10^{-3}	5×10^{-4}	1×10^{-4}	4.8×10^{-3}	6.6×10^{-3}	296
Beginning of November 2024: start of dasatinib monotherapy										
16	Nov 2024	1 month later	1×10^{-4}	1×10^{-4}	neg	5×10^{-4}	1×10^{-5}	pos $<5\times10^{-4}$	1.8×10^{-3}	21
17	Jan 2025	3 months later	1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-4}	pos $<1\times10^{-4}$	4.9×10^{-4}	3
18	Apr 2025	5.5 months later	1×10^{-4}	1×10^{-4}	neg	5×10^{-4}	1×10^{-4}	neg	na	3
19	Aug 2025	10 months later	1×10^{-4}	1×10^{-5}	neg	1×10^{-4}	1×10^{-5}	neg	na	2

Note: The EsPhALL2017/COGAALL1631 protocol has been granted ethical approval and written informed consent was signed by parents/tutors of each enrolled patient. The columns 'IgH VH4 JH6' and 'IgH VH1 JH6' show IG/TR DNA MRD results; the column '*BCR::ABL1* DNA' shows DNA MRD results on genomic fusion breakpoint and the column '*BCR::ABL1* RNA' real-time quantitative polymerase chain reaction (qPCR) of transcript levels based on RNA analysis. IG/TR PCR MRD negativity was achieved at EOC, leading to standard risk treatment (Arm B-COG) without indication for HSCT in CR1. After treatment completion, MRD monitoring was continued at the request of the patient's family. *BCR::ABL1* MRD levels were monitored every 3–4 months for 3 years after stop therapy and ranged from 0.01% to 4.77%. IG/TR PCR MRD became detectable only at the beginning of year 3, gradually increasing up to 4.7×10^{-3} (with a concomitant FCM MRD low positivity of 0.043%) at 5 years after initial Ph+ ALL diagnosis. Dasatinib monotherapy was re-initiated at this time, and the patient remains in IG/TR PCR MRD-negative CR with minimal *BCR::ABL1* MRD positivity (0.02%).
Abbreviations: EOC, end of consolidation; EOI, end of induction; na, not available; neg, negative; pos, positive; QR, quantitative range; SR, sensitive range.

Relapse patterns have also changed in the TKI era, with the majority of relapses now occurring after chemotherapy completion compared to ~30% at ≥30 months from diagnosis in the pre-TKI era.[2] Indeed, we are aware of three children with Ph+ ALL who relapsed more than 9 years from initial diagnosis (Biondi, Zuna and Loh, personal communication), including one with CML-like disease. Whether prolonged TKI monotherapy would have altered this relapse risk remains unknown.

An international 'Ponte di Legno' initiative has accordingly been launched to collect real-world data on TKI use after completion of conventional chemotherapy in paediatric Ph+ ALL and to evaluate efficacy of salvage therapies following 'relapse' by either standard criteria or by low-level emergence/persistence of MRD.

To optimally assess clinical outcomes, details regarding subsequent treatment interventions and prolonged follow-up are needed, which is challenging due to disease rarity and operational burden. Most clinical trials do not routinely capture data after front-line therapy and post-HSCT, partly due to patients being referred to adult institutions for continued care. Robust collection of long-term outcomes may ultimately require a formal registry rather than clinical trials. A more ambitious approach, aimed at optimizing therapeutic plans, calls for adaptive trial designs as in the Sequential, Multiple Assignment, Randomized Trials (SMART),[14] which adopt a structured sequence of diagnostic/therapeutic strategies enabling, for instance, the incorporation of innovative treatments for first/impending relapse.

The ICH E9(R1) guidelines (see references in Supplementary Material) provide a framework for statistical analysis in the presence of intercurrent events, defined as 'events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest'. While the primary estimand (end-point) in Ph+ ALL studies is usually

EFS, measured as the time from diagnosis to resistance, relapse, second malignancy or death (whichever occurs first), in future study designs this could incorporate intercurrent events based on additional MRD evaluations during follow-up. This approach could produce a more granular EFS definition, enriching this composite variable with another mode of failure, such as 'impending relapse', based on clear time-point(s), cut-offs and MRD assay. For example, the patient described in Table 2 would be considered alive in CR by standard EFS, whereas counted as having an event under this alternative approach. To ensure comparability of results with previous trials, the standard EFS could be added as a sensitivity analysis to the 'enriched' EFS. Furthermore, the competing risk approach could be used to estimate the contribution of each EFS component, thus shedding light on the impact of each cause of failure.

In conclusion, successful TKI-based therapies during the past two decades have transformed clinical outcomes of children with Ph+ ALL and established a new precedent for precision medicine approaches for other high-risk subtypes of childhood ALL. Recent additional advances in treatment of adult Ph+ ALL (see references in Supplementary Material), particularly intercalation of blinatumomab immunotherapy, reduction of toxic chemotherapy and credentialing of next-generation TKIs,[15] challenge paediatric haematologists to investigate similar strategies in children and adolescents. A first step in this direction is the ongoing AALL2131/EsPhALL2022 international study. Efforts should also be made to collect robust information regarding long-term outcomes both from clinical trials and real-world data and to adopt novel statistical approaches to study design and analysis, with the overarching goal of further reducing relapse risk and improving long-term survival with less toxicity.

AUTHOR CONTRIBUTIONS

ABa, MGV, ABi, LBS, THT, SKT, SPH, VG and PDL designed the study and wrote the manuscript; all authors reviewed and approved the final manuscript.

KEYWORDS

immunotherapy, intercurrent events, long-term outcomes, minimal residual disease, paediatric Ph+ALL, tyrosine kinase inhibitors

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CONFLICT OF INTEREST STATEMENT

SKT receives research funding from Incyte Corporation and Kura Oncology; serves/d on scientific advisory boards for Aleta Biotherapeutics, Amgen, Ascentage Pharmaceuticals, AstraZeneca, C-Further/LifeArc, Kura Oncology, Novartis Pharmaceuticals and Syndax Pharmaceuticals; and has received travel support from Amgen and Jazz Pharmaceuticals (all for unrelated studies). SPH owns common stock in Amgen and has received honoraria from Jazz and Servier. RP has participated in advisory board meetings for Amgen, Novartis, Clinigen and Jazz Pharma and has received honoraria from Amgen for the speaker bureau. GC (or the institution) has received research support or honoraria or travel support from Amgen, Clinigen and Jazz Pharma. The other authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was performed according to the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

This manuscript does not report identifiable patient information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.