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Received: September 21, 2026.

Accepted: September 23, 2026.

Citation: Marlise R. Luskin and Lori Muffly.

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Haematologica. 2026 Oct 1. doi: 10.3324/haematol.2026.301958 [Epub ahead of print]

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## **Philadelphia chromosome-like acute lymphoblastic leukemia: treat intensively, transplant selectively**

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**Author contributions:** MRL and LM wrote the editorial.

### **LM Disclosures:**

**Research Funding:** Kite, Autolus, Incyte, Imviva/Bioheng, Orca Bio, Adaptive

**Advisory Boards:** Autolus, Incyte, Orca Bio, Syndax, Medexus, Merck

**Honoraria:** Autolus, Kite, Orca Bio

### **MRL Disclosures:**

**Research Funding:** Novartis, AbbVie

**Advisory Boards/Consulting:** AbbVie, Amgen, Astra Zeneca, Autolus, Enliven, Jazz, KITE, Menarini Stemline, Merck, Novartis, Servier, Syndax

In this issue of *Haematologica*, Aldoss and colleagues shed light on how to treat Philadelphia chromosome-like (Ph-like) acute lymphoblastic leukemia (ALL), a famously high-risk subtype of ALL that often challenges leukemia clinicians.<sup>1</sup>

Ph-like ALL is a heterogeneous group of ALL subtypes characterized by activated kinase and cytokine-receptor signaling but unified by a gene-expression profile resembling Philadelphia chromosome-positive ALL.<sup>2,3</sup> As a group, Ph-like ALL confers adverse risk in both children and adults because of its frequent resistance to chemotherapy.<sup>3-5</sup> Patients with Ph-like ALL commonly have persistent measurable residual disease (MRD) after induction or early consolidation and are more likely to relapse after achieving initial complete remission (CR).<sup>3-6</sup> Ph-like ALL can affect patients of any age or ethnicity, but is particularly prevalent among Hispanic adolescents and young adults (AYAs), in part because of enrichment of a *GATA3* polymorphism.<sup>7</sup>

The association of Ph-like ALL with adverse outcomes is well established in adult ALL; however, optimal management remains unclear. In children, treatment is risk-adapted according to MRD response.<sup>8</sup> In adults, in contrast, allogeneic hematopoietic stem cell transplantation (HCT) is often recommended in first complete remission (CR1) regardless of initial treatment response. Additionally, uncertainty persists regarding the optimal chemotherapy backbone, and how treatment should be modified in the modern era of blinatumomab. Here, Aldoss and colleagues leverage their extensive experience treating Ph-like ALL to help address these questions.

This study analyzed a large, single-center cohort of 140 primarily young adults (median age 33.5 years; 17% aged  $\geq 55$  years) with Ph-like ALL initially treated at City of Hope (COH) between 2014 and 2026. Most patients were of Hispanic ethnicity (87%), and most had *CRLF2*-rearranged ALL ( $n=120$ , 85%; *IGH::CRLF2* or *P2RY8::CRLF2*). The investigators examined the impact of patient, disease, and treatment characteristics on initial response, relapse, and survival. Although the use of blinatumomab and HCT evolved over the study period, the authors attempted to account for treatment heterogeneity and reached several conclusions with potential relevance to clinical practice.

First, patients who received induction with a pediatric-inspired regimen (PIR) were more likely to achieve CR than those receiving hyper-CVAD (83% versus 53%). Treatment was not randomly assigned, and the 75% of patients receiving a PIR were significantly younger than those receiving hyper-CVAD or other regimens. Nevertheless, multivariable analysis supported the finding: non-PIR regimens remained associated with lower likelihood of CR (adjusted OR: 0.36,  $p=0.034$ ). Unadjusted analyses also showed superior relapse-free survival (RFS) and overall survival (OS) and decreased cumulative incidence of relapse (CIR) among PIR-treated patients, findings that persisted in adjusted analyses. Within the inherent limitations of a retrospective study, the COH experience supports an asparaginase-based PIR as initial therapy for younger adults with Ph-like ALL.

A second, often vexing question for leukemia clinicians, is which patients with Ph-like ALL should undergo HCT in CR1. In the COH cohort, 27 patients had persistent MRD after chemotherapy. Blinatumomab cleared MRD in all but one patient (96%), a very high rate of MRD conversion consistent with other reports.<sup>9</sup> Most then underwent HCT; only six did not, three of whom have relapsed to date. The recently published GIMEMA LAL2317 study showed that that effective MRD clearance with blinatumomab does not overcome the adverse prognosis associated with pre-blinatumomab MRD. Together, these observations support continuing to recommend HCT for patients with Ph-like ALL and persistent MRD after chemotherapy once MRD is cleared with blinatumomab.

More uncertain is whether patients with Ph-like ALL who achieve early MRD clearance following initial chemotherapy might also benefit from HCT in CR1. In this cohort, 65 younger, transplant-eligible patients achieved MRD-negative CR by multiparameter flow cytometry (MFC; sensitivity  $10^{-4}$ ); approximately half underwent transplant ( $n=33$ ) while the other half continued chemotherapy ( $n=32$ ). In a 180-day landmark analysis designed to address immortal time bias and including of 51 of the 65 patients, HCT was not associated with improvement in CIR, RFS, or OS in either unadjusted or adjusted Cox proportional hazards models. These findings support extending the pediatric paradigm to adults by using MRD response, rather than Ph-like status alone, to guide HCT decisions in CR1.

Further evidence comes from a cohort of 17 patients who achieved early MRD negativity by next-generation sequencing (NGS; sensitivity  $10^{-6}$ ). Fourteen did not undergo HCT, and with a median follow-up of 10.5 months, only one patient has relapsed. Although this is a small cohort with limited follow-up, the findings suggest that achievement of a deep remission after chemotherapy may identify patients with Ph-like ALL with favorable disease biology who can safely forgo HCT in CR1, particularly when receiving a PIR and blinatumomab.<sup>10</sup>

Of course, new findings inevitably generate additional questions. This study does not establish how to manage patients who are MRD-negative by MFC ( $10^{-4}$ ) but remain MRD-positive by NGS ( $10^{-6}$ ). In addition, the investigators' conclusions were derived from a cohort of younger, predominantly Hispanic ethnicity patients with *CRLF2*-rearranged leukemia treated with PIRs at a large and experienced leukemia center. Whether the same MRD-adapted approach applies to older patients receiving hyper-CVAD or other non-PIR approaches, or to patients with non-*CRLF2*-rearranged Ph-like ALL, including ABL-class or *EPOR*-rearranged disease, is uncertain. Another key question is how to select patients for HCT when immunotherapy, including inotuzumab and/or blinatumomab, is incorporated even earlier in frontline treatment, such that most patients clear MRD during the initial weeks of treatments.

In summary, despite the limitations of a retrospective single-center analysis, this study by Aldoss and colleagues provides clinically useful guidance. The findings reinforce the value of intensive PIRs for younger patients with Ph-like ALL and support tailoring transplant decisions according to disease biology as revealed by MRD response. Future studies—ideally prospective and multicenter, encompassing diverse Ph-like genomic

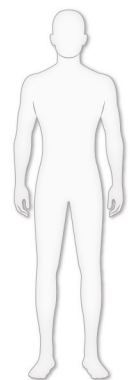
subtypes, modern immunotherapy-based regimens, and highly sensitive MRD assessment—will be essential to refine these conclusions and further guide clinicians caring for patients with Ph-like ALL.

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Legend to figure

A path for personalizing treatment of Philadelphia chromosome-like acute lymphoblastic leukemia



Patient with  
Ph-like ALL

**Pediatric-  
inspired  
regimen (PIR)**  
(asparaginase-  
based  
chemotherapy)



**MRD  
assessment**

**MRD+**

**Blinatumomab**



**Allogeneic  
transplant**



**MRD-**

**Blinatumomab**



**More  
chemotherapy**



**Induction**

**MRD-guided decision**

**Consolidation and beyond**