CORRESPONDENCE OPEN

Check for updates

Allogeneic stem cell transplantation in adult Ph-like acute lymphoblastic leukemia. Results from two consecutive GIMEMA protocols

Bone Marrow Transplantation; https://doi.org/10.1038/s41409-026-02966-2

To the Editor,

BCR::ABL1-like acute lymphoblastic leukemia, also referred to as Ph-like ALL, is a heterogeneous subtype of B-cell precursor ALL (BCP-ALL) with a gene-expression profile resembling BCR::ABL1-positive ALL, despite lacking the BCR::ABL1 fusion. It is enriched for kinase-activating lesions and is associated with adverse prognosis in pediatric and adult cohorts [1–3]. In adults, its incidence increases with age and may reach approximately 30% in older patients [4]. Although the Ph-like signature can identify patients with potentially targetable lesions, routine detection remains challenging because gene-expression profiling and RNA sequencing are not universally available. To facilitate the identification of Ph-like cases, Chiaretti et al. developed the "BCR/ABL1-like predictor", a quantitative real-time PCR-based tool relying on the expression levels of 10 genes and showing high sensitivity and specificity as a surrogate diagnostic approach [5]. The optimal post-remission strategy for adult Ph-like ALL remains incompletely defined. In particular, although allogeneic hematopoietic stem cell transplantation (alloHSCT) is an effective consolidation strategy for high-risk or chemoresistant ALL, its specific role in Ph-like ALL has not been conclusively established.

We therefore evaluated the clinical impact of the Ph-like signature and the role of alloHSCT in adult BCP-ALL patients enrolled in two consecutive prospective GIMEMA trials, LAL1913 and LAL2317 [6, 7]. Both protocols included pediatric-inspired intensive chemotherapy; in LAL2317, two courses of blinatumomab were added after consolidation cycles 3 and 6. Eligibility for alloHSCT in complete hematologic remission was based on predefined high-risk features at diagnosis and/or minimal residual disease (MRD) positivity during treatment [6, 7]. Ph-like status was assessed retrospectively for translational research purposes using the BCR/ABL1-like predictor on diagnostic samples and was not itself used as an indication for transplantation. Patients signed an informed consent form in accordance with the Helsinki Declaration, and both protocols were approved by the Ethics Committees of all participating Institutions.

Among 199 evaluable BCR::ABL1-negative, KMT2A/AFF1-negative, and TCF3/PBX1-negative BCP-ALL patients, 59 cases (30%) fulfilled criteria for a Ph-like signature. Overall 88 patients were enrolled in LAL1913 and 111 in LAL2317. Among Ph-like cases, ABL-class alterations were detected in 9 patients, CRLF2 alterations in 21, and JAK2 rearrangements in 6; in the remaining 23 cases, no specific kinase-activating alteration was identified. Baseline characteristics were generally comparable between Ph-like and non-Ph-like patients. However, Ph-like ALL was associated with a higher frequency of WBC $> 30 \times 10^9$/L and a higher prevalence of IKZF1 and IKZF1plus deletions (Supplementary Table 1), consistent with previous observations [2, 3]. The complete hematologic remission rate after induction was similar in Ph-like and non-Ph-like patients. However, among patients alive after induction, refractory disease was numerically more frequent in the Ph-like group (12% vs 4%). At week 10, the pivotal MRD timepoint for transplant allocation, MRD negativity was less frequent among Ph-like patients (63% vs 77%). With a median follow-up of 39.5 months, Ph-like ALL was associated with significantly inferior outcomes, with a 3-year disease-free survival (DFS) of 38% compared with 75% in non-Ph-like ALL ($p < 0.001$), and a 3-year overall survival (OS) of 51% compared with 72% ($p = 0.032$), respectively (Supplementary Fig. 1A, B). These findings confirm the adverse prognostic impact of the Ph-like signature in adult BCP-ALL, even within modern pediatric-inspired, MRD-oriented programs. A larger proportion of Ph-like patients had an indication for alloHSCT compared with non-Ph-like patients (33/59, 56% vs 48/140, 34%, $p = 0.0042$). Overall, 22 Ph-like patients proceeded to transplantation, mainly because of very high-risk features at diagnosis or MRD positivity; a minority underwent alloHSCT according to the investigator's decision. In the LAL2317 protocol, only 30% of patients receiving blinatumomab were allocated to transplantation due to MRD positivity, compared with 50% in the LAL1913 protocol. Among the 11 patients allocated to alloHSCT who did not undergo transplantation, the reasons were early relapse ($n = 4$), physician decision ($n = 2$), toxicity from prior therapy ($n = 1$), donor unavailability ($n = 1$), patient preference ($n = 1$), and unknown ($n = 2$).

Most transplanted patients received myeloablative conditioning (91%), and 50% received a total body irradiation-based regimen. Donors included matched sibling (50%), matched unrelated (5%), mismatched unrelated (18%), or haploidentical (27%). When Ph-like patients who underwent alloHSCT were compared with those who did not, survival appeared similar (Supplementary Fig. 2A, B). This observation should be interpreted in light of the higher-risk profile of patients selected for transplant. To better account for treatment allocation and the time-dependent nature of transplantation, we performed an intention-to-treat analysis using Simon-Makuch methodology. Among Ph-like patients allocated to alloHSCT, those who actually received the procedure had superior outcomes compared with those who did not, with a 3-year DFS of 31% versus 0% ($p = 0.0085$) and OS of 47.1% versus 19.3% (0.0334) (Fig. 1A, B). These data support alloHSCT as a relevant therapeutic option for eligible Ph-like ALL patients with high-risk features at diagnosis or MRD positivity during chemotherapy, in line with previous reports [8, 9]. Nevertheless, outcomes remained unsatisfactory, underscoring the need for improved disease control before and after

Received: 18 March 2026 Revised: 24 May 2026 Accepted: 23 June 2026
Published online: 08 July 2026

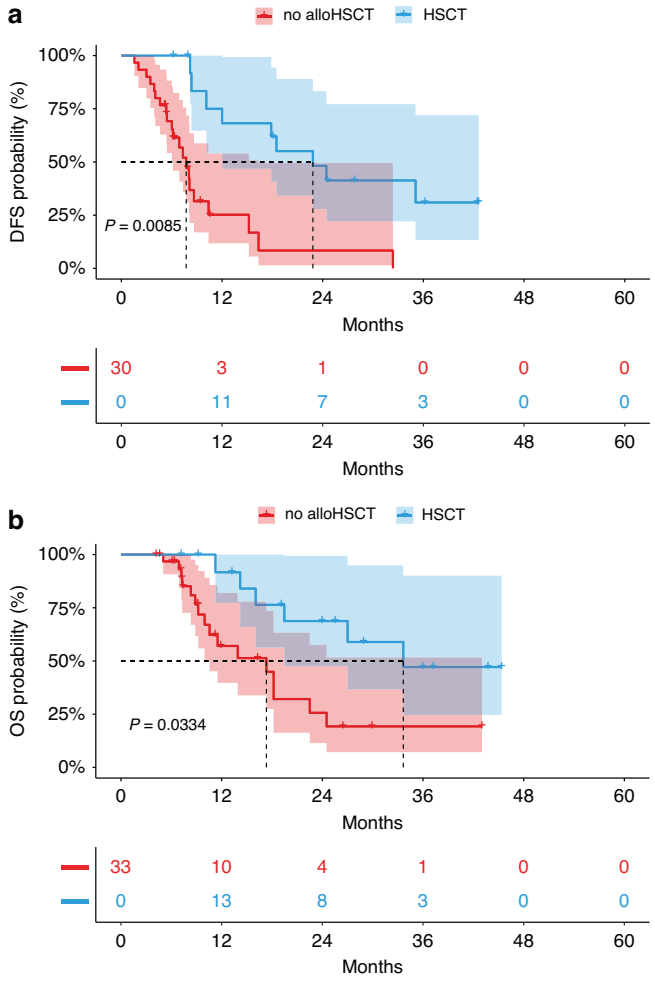

Fig. 1 Disease free survival and overall survival of Ph-like ALL allocated to transplant. a Simon Makuch plot for disease-free survival of Ph-like ALL patients allocated to transplant, whether they underwent the procedure or not. **b** Simon Makuch's plot for the overall survival of Ph-like ALL patients allocated to transplant, whether they underwent the procedure or not.

transplantation. In LAL2317, the addition of a limited number of blinatumomab cycles improved MRD clearance in the overall study population [7], but this strategy may have been insufficient for biologically high-risk subsets such as Ph-like ALL. Recent data suggest that broader incorporation of blinatumomab may improve outcomes in adult BCP-ALL, including high-risk and MRD-negative patients [10]. In parallel, early identification of Ph-like ALL is essential to guide targeted therapy, particularly tyrosine kinase inhibitors in patients with ABL-class rearrangements. Such strategies may increase the depth of molecular response before alloHSCT and potentially reduce relapse risk after transplantation. Post-transplant interventions, including targeted early maintenance, rapid tapering of immunosuppression, prophylactic or pre-emptive donor lymphocyte infusions, and post-transplant immunotherapeutic approaches with blinatumomab or inotuzumab, warrant prospective evaluation. Donor-derived cellular therapies may also become relevant in selected patients [11, 12].

This analysis has several strengths, including the inclusion of patients treated within prospective multicenter trials using pediatric-inspired regimens, centralized MRD assessment, and predefined MRD timepoints for therapeutic decisions. However, important limitations must be acknowledged. First, Ph-like status was assessed retrospectively and was not incorporated into the original transplant risk algorithm. Second, Ph-like identification relied on the BCR/ABL1-like predictor, a practical surrogate tool that may be less comprehensive than gene-expression profiling or RNA sequencing. Third, the number of Ph-like patients was limited, reducing the statistical power to draw definitive conclusions. Finally, neither trial was specifically designed to assess the effect of alloHSCT in Ph-like ALL, and several transplant-related variables, including donor choice, graft source, conditioning intensity, and use of total body irradiation, were determined according to institutional policy.

In conclusion, our findings confirm the adverse prognostic impact of the Ph-like signature in adult BCP-ALL and support the continued consideration of alloHSCT as a consolidation strategy for Ph-like patients with high-risk features or persistent MRD. Future studies should focus on early diagnostic identification, integration of targeted therapies and immunotherapy before transplantation, and post-transplant relapse-prevention strategies. In this regard, the GIMEMA ALL2922 study, designed to identify Ph-like ALL at diagnosis and optimize treatment through the addition of ponatinib, has recently completed enrolment and may provide further insight into the management of this high-risk subgroup.

Federico Lussana[1,2,19]✉, Giuliana Rizzuto[2,19], Alfonso Piciocchi[3], Elena Oldani[2], Francesca Kaiser[4], Orietta Spinelli[2], Anna Grassi[2], Irene Della Starza[4], Alessandra Santoro[5], Deborah Cardinali[4], Marco Beldinanzi[4], Erika Borlenghi[6], Monica Bocchia[7], Paolo De Fabritiis[8], Anna Candoni[9,10], Felicetto Ferrara[11], Prassede Salutari[12], Monia Lunghi[13], Fabio Giglio[14], Massimo Martino[15], Mariangela Di Trani[4], Valentina Arena[3], Monica Messina[3], Renato Bassan[16], Alessandro Rambaldi[1,17], Robin Foà[4], Francesca Bonifazi[18,20] and Sabina Chiaretti[4,20]

[1]Department of Oncology and Hematology, University of Milan, Milan, Italy. [2]Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy. [3]GIMEMA Foundation, Rome, Italy. [4]Division of Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy. [5]Division of Hematology, Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy. [6]Operational Unit of Hematology, Azienda Socio Sanitaria Territoriale Spedali Civili, Brescia, Italy. [7]Hematology Unit Azienda Ospedaliero-Universitaria Senese, University of Siena, Siena, Italy. [8]Complex Operational Unit of Hematology, Ospedale S. Eugenio ASL Roma 2, University of Tor Vergata, Rome, Italy. [9]Department of Hematology, Azienda Ospedaliero-Universitaria, Udine, Italy. [10]Università degli Studi di Modena e Reggio Emilia, Modena, Italy. [11]Division of Hematology, Cardarelli Hospital, Naples, Italy. [12]Operational Unit of Clinical Hematology, Azienda USL, Pescara, Italy. [13]Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy. [14]Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele Scientific Institute, Milan, Italy. [15]Stem Cell Transplantation and Cellular Therapies Unit, Grande Ospedale Metropolitano, BMM, Reggio Calabria, Italy. [16]Complex Operational Unit of Hematology, Ospedale dell'Angelo and Ospedale SS Giovanni e Paolo, Venezia, Italy. [17]Foundation of Clinical Research-FROM Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy. [18]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. [19]These authors contributed equally: Federico Lussana, Giuliana Rizzuto. [20]These authors jointly supervised: Francesca Bonifazi, Sabina Chiaretti. ✉email: flussana@asst-pg23.it

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Chiaretti S, Li X, Gentleman R, Vitale A, Wang KS, Mandelli F, et al. Gene expression profiles of B-lineage adult acute lymphocytic leukemia reveal genetic patterns that identify lineage derivation and distinct mechanisms of transformation. Clin Cancer Res. 2005;11:7209–19. https://doi.org/10.1158/1078-0432.CCR-04-2165.
2. Mullighan CG, Collins-Underwood JR, Phillips LAA, Loudin MG, Liu W, Zhang J, et al. Rearrangement of CRLF2 in B-progenitor and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet. 2009;41:1243–6. https://doi.org/10.1038/ng.469.
3. Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol. 2009;10:125–34. https://doi.org/10.1016/S1470-2045(08)70339-5.
4. Tasian SK, Hurtz C, Wertheim GB, Bailey NG, Lim MS, Harvey RC, et al. High incidence of Philadelphia chromosome-like acute lymphoblastic leukemia in older adults with B-ALL. Leukemia. 2017;31:981–4. https://doi.org/10.1038/leu.2016.375.
5. Chiaretti S, Messina M, Grammatico S, Piciocchi A, Fedullo AL, Di Giacomo F, et al. Rapid identification of BCR/ABL1-like acute lymphoblastic leukaemia patients using a predictive statistical model based on quantitative real-time-polymerase chain reaction: clinical, prognostic and therapeutic implications. Br J Haematol. 2018;181:642–52. https://doi.org/10.1111/bjh.15251.
6. Bassan R, Chiaretti S, Della Starza I, Spinelli O, Santoro A, Paoloni FP, et al. Pegaspargase-modified risk-oriented program for adult acute lymphoblastic leukemia: results of the GIMEMA LAL1913 trial. Blood Adv. 2023;7:4448–61. https://doi.org/10.1182/bloodadvances.2022009596.
7. Bassan R, Chiaretti S, Della Starza I, Santoro A, Spinelli O, Tosi M, et al. Upfront blinatumomab improves MRD clearance and outcome in adult Ph- B-lineage ALL. The GIMEMA LAL2317 phase 2 study. Blood. 2025;145:2447 https://doi.org/10.1182/blood.2024027500.
8. Aldoss I, Yang D, Tomasian V, Mokhtari S, Jackson R, Gu Z, et al. Outcomes of allogeneic hematopoietic cell transplantation in adults with fusions associated with Ph-like ALL. Blood Adv. 2022;6:4936–48. https://doi.org/10.1182/bloodadvances.2022007597.
9. Rahman ZA, Othman T, Saliba RM, Alejandra Y, Vanegas M, Mohty R, et al. Transplantation and cellular therapy allogeneic à adult a multicenter analysis of allogeneic transplant outcomes in adults with Philadelphia-like B-cell acute lymphoblastic leukemia in first complete remission. Transpl Cell Ther. 2024;30:1197–205. https://doi.org/10.1016/j.jtct.2024.09.020.
10. Litzow MR, Sun Z, Mattison RJ, Paietta EM, Roberts KG, Zhang Y, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. N Engl J Med. 2024;391:320–33. https://doi.org/10.1056/nejmoa2312948.
11. Lussana F, Magnani CF, Galimberti S, Gritti G, Gaipa G, Belotti D, et al. Donor-derived CARCIK-CD19 cells engineered with Sleeping Beauty transposon in acute lymphoblastic leukemia relapsed after allogeneic transplantation. Blood Cancer J. 2025;15:1–14. https://doi.org/10.1038/s41408-025-01260-6.
12. Roddie C, Dias J, O'Reilly MA, Abbasian M, Cadinanos-Garai A, Vispute K, et al. Matched donor allogeneic CAR-T for adult B-ALL: toxicity, efficacy, repeat dosing, and the importance of lymphodepletion. Blood. 2025;146:1664–76. https://doi.org/10.1182/blood.2025028790.

AUTHOR CONTRIBUTIONS

FL and GR designed the study, collaborated in data interpretation, wrote the test and gave the final approval before manuscript submission; AP, MM, and VA analysed the data, collaborated in data interpretation, revised the manuscript and gave the final approval before manuscript submission; FK, AG, AS, EB, MoB, PDeF, AC, FF, PS, ML, FG, and MaM are part of the medical team who has followed patients, collected clinical data, revised the manuscript and gave the final approval before manuscript submission; EO integrated data, revised the manuscript and gave the final approval before manuscript submission; OS, IDS, MB, DC, and MDT performed the laboratory tests (MRD and Ph-like signature), collaborated in data interpretation, revised the manuscript and gave the final approval before manuscript submission; RB, AR, RF, FB and SC designed the study, collaborated in data interpretation, provided major intellectual contribution to the preparation of the manuscript and gave the final approval before manuscript submission.

FUNDING STATEMENTS

This work was supported by Associazione Italiana Ricerca sul Cancro (AIRC), Special 5 × 1000 Program "Metastatic disease: the key unmet need in oncology"-ISM-Code:21147 to AR and the Associazione Italiana Lotta alla Leucemia, Linfoma e Mieloma (AIL) Sezione Bergamo**;** Associazione Italiana per la Ricerca sul Cancro (AIRC) 5 × 1000, Special Program Metastases (21198), Milan (Italy) to RF; Progetti di Rilevante Interesse Nazionale (PRIN) Italia, 20222EC7LA project to SC.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-026-02966-2.

Correspondence and requests for materials should be addressed to Federico Lussana.