ARTICLE

Non-inferior long-term outcomes of adults with Philadelphia chromosome-like acute lymphoblastic leukemia

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Abstract

Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) is associated with inferior outcomes in the chemotherapy setting. We hypothesized that allogeneic hematopoietic cell transplantation (allo-HCT)-based post-remission therapy would improve outcomes of this entity. We examined the frequency and long-term outcomes of adults with Ph-like ALL, particularly focusing on allo-HCT outcomes for Ph-like ALL versus non-Ph-like ALL. Ph-like ALL was determined by anchored multiplex PCR-based targeted next-generation sequencing. Of the 344 patients, 57 (16.6%) had Ph-like ALL, 197 (57.3%) had Ph-positive ALL, and 90 (26.1%) had B-other ALL. To further evaluate the prognosis of Ph-like ALL, outcome analyses were restricted to 147 patients, excluding Ph-positive ALL. The actual allo-HCT rates in complete remission were 87.7% for Ph-like ALL, 71.4% for B-other standard-risk ALL, and 70.4% for B-other poor-risk ALL. Patients with Ph-like ALL had a higher 5-year overall survival (60.6% vs 27.1%; $P = 0.008$) than B-other poor-risk ALL subgroup, while no difference was observed compared with B-other standard-risk ALL subgroup. Similar results were noted in a separate analysis for patients receiving allo-HCT in complete remission. In multivariate analyses, B-other poor-risk ALL was associated with poorer outcomes. Our data showed that allo-HCT-based post-remission therapy may have contributed to non-inferior outcomes of adult Ph-like ALL.

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Introduction

Compared with children with B-cell precursor acute lymphoblastic leukemia (BCP-ALL), overall treatment outcomes of adults with BCP-ALL remain suboptimal with a long-term disease-free survival (DFS) of 40–50% [1, 2]. This discrepancy can be attributed in part to the higher frequency of adverse genetic abnormalities (such as *BCR-ABL1* translocation, *KMT2A* rearrangements, or complex karyotypes) and poorer tolerance to intensive chemotherapy in adults [3]. Based on genome-wide analysis, *BCR-ABL1*-like or Philadelphia chromosome (Ph)-like ALL was identified as a high-risk subtype of BCP-ALL which has a gene expression profile similar to Ph-positive ALL but lacks the *BCR-ABL1* fusion protein [4, 5]. This new category is not an uncommon entity, and has a heterogeneous genetic background [6]. Subsequent studies have unveiled its characteristic genetic abnormalities including *CRLF2* rearrangements and mutations, ABL-class rearrangements, *JAK2* or *EPOR* rearrangements, mutations activating JAK-STAT signaling and RAS signaling, and uncommon kinase alterations [7–9]. Some genetic abnormalities can be
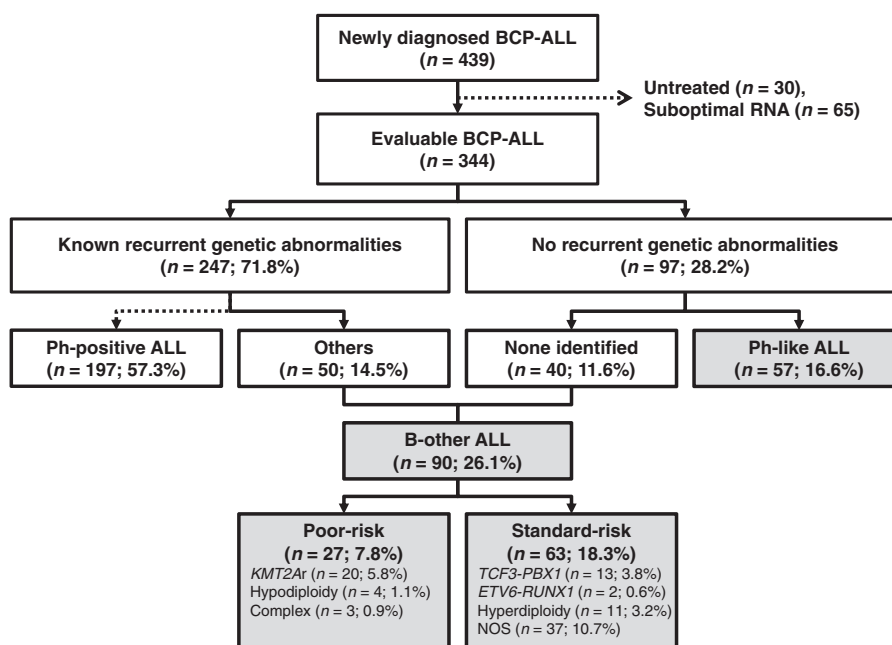
therapeutic targets of tyrosine kinase inhibitors (TKIs) [10, 11]. However, data from adults with Ph-like ALL are still limited, and no data have yet been introduced in Asian population.

Ph-like ALL is associated with inferior outcomes across all ages. Several studies of patients with Ph-like ALL have shown a higher post-induction minimal residual disease (MRD) levels compared with other subgroups of BCP-ALL [5, 9, 12–15], and this translates into inferior outcomes in the conventional chemotherapy setting [5, 9, 12, 13, 15]. However, Ph-like ALL is a heterogenous subtype that may not all share the same adverse impact on prognosis. Therefore, the inferior outcomes of chemotherapy for adult Ph-like ALL raise a question on the role of allogeneic hematopoietic cell transplantation (allo-HCT) in preventing relapse and improving outcomes. The role of allo-HCT in adults with Ph-like ALL remains unclear because of a lack of studies in this genetic subgroup.

Here, we tried to identify the frequency, genetic characteristics, and long-term outcomes of adults with Ph-like ALL who were treated with the same treatment policy at a single, the largest institution in Korea. Furthermore, we particularly focused on allo-HCT outcomes for Ph-like ALL versus non-Ph-like ALL.

Methods

Patients

Between December 2008 and March 2016, 344 adults (median age, 43 years [range, 15–74 years]) with newly diagnosed BCP-ALL who received a uniform frontline chemotherapy and had suitable material for genomic analysis were evaluable for this retrospective analysis (Fig. 1). A total of 95 patients who did not receive frontline chemotherapy ($n = 30$) or had suboptimal RNA ($n = 65$) were excluded. Additionally, since the use of TKIs has significantly changed the treatment paradigm and prognosis of Ph-positive ALL, 197 patients with Ph-positive ALL were further excluded (but not for frequency calculation) to better evaluate long-term outcomes and prognosis of Ph-like ALL compared with Ph-negative, non-Ph-like BCP-ALL. Thus, a total of 147 adults with Ph-negative BCP-ALL were included in the final outcome analysis reported here. The routine diagnostic work-up included bone marrow pathology, immunophenotyping, cytogenetics, and molecular genetics according to the WHO classification [3]. Patients were categorized as (1) Ph-like ALL, (2) B-other ALL with poor-risk cytogenetics (*KMT2A* rearrangements, hypodiploidy, complex karyotype [≥5 chromosomal abnormalities]), and (3) B-other ALL with standard-risk cytogenetics. All patients provided written informed consent approved by the institutional review board of the Catholic University of Korea (KC17SESI0717). This study was conducted in accordance with the Declaration of Helsinki.

Treatment schedule

The treatment schedule is summarized in Supplementary Fig. S1. As described in our previous studies [16–18], induction chemotherapy was started with hyper-fractionated cyclophosphamide (300 mg/m^2, every 12 h, days 1–3), vincristine (1.4 mg/m^2, maximum dose 2 mg/day, days 4

and 11), daunorubicin (45 mg/m^2/day, days 4 and 11), and dexamethasone (40 mg/day, days 1–4 and days 11–14). Then, patients received subsequent chemotherapy courses consisting of high-dose cytarabine (2 g/m^2, every 12 h, days 1–5) and mitoxantrone (12 mg/m^2/day, days 1–2) therapy (at each odd cycle) alternating with the above induction regimen (at each even cycle). Central nervous system prophylaxis was performed by intrathecal administration of triple agents (methotrexate 12 mg, cytarabine 40 mg, and hydrocortisone 50 mg; 6 times in total). Patients with a donor proceeded to HCT as early as possible. Patients unable to undergo HCT received continuous chemotherapy followed by maintenance treatment consisting of 6-mercaptopurine (50 mg/m^2, daily), vincristine (1.4 mg/m^2, maximum 2 mg, day 1, every 4 weeks), and predisolone (40 mg/m^2 × 7 days, every 4 weeks) for 2 years. None were treated with TKIs during chemotherapy courses and post-HCT period.

Transplantation policy

Our center offers allo-HCT according to donor availability as a post-remission treatment for adult ALL. Donor-recipient pairs are considered matched when the pair is identical at HLA-A, -B, -C and -DRB1 loci with high-resolution HLA genotyping. If a matched sibling donor is available, HCT is offered, irrespective of risk assessment. Patients who have no available sibling donor, especially those with high-risk features, are offered to receive matched or 1-allele-mismatched unrelated donor transplantations, which is dependent on the speed of coordination process. For patients without a suitable unrelated donor, cord blood (CB) was mainly selected based on our center's criteria. Some patients without high-risk features underwent transplantation according to patient preference. For CBT, minimum HLA typing requirements followed the current practice of low-resolution typing for HLA-A and -B and high-resolution typing of HLA-DRB1. CB units were matched at a minimum of 4/6 loci and contained total nucleated cells at least 3.0 × 10^7/kg. When a single CB unit with adequate cell dose was not available, double CBT was performed. Data from haploidentical transplantation were not included in this analysis because it has been possible under the national reimbursement system in Korea since 2016.

As previously described [16–18], to be eligible for myeloablative conditioning, patients had to be younger than 50 years with no signs of organ dysfunction or active infections. The myeloablative conditioning regimen consisted of total body irradiation (TBI, 13.2 Gy) and cyclophosphamide (120 mg/kg). Patients of an advanced age (≥50 years) or with comorbid conditions were given a reduced-intensity conditioning regimen consisted of

fludarabine (150 mg/m^2) and melphalan (140 mg/m^2). Graft-versus-host disease (GVHD) prophylaxis was attempted by administering calcineurin inhibitors (cyclosporine for sibling transplants and tacrolimus for unrelated transplants) and methotrexate. For CBT, tacrolimus and mycophenolate mofetil were used for GVHD prophylaxis. In all transplants, immunosuppressants were gradually tapered from day 90 and in the absence of GVHD discontinued 6 months after HCT. Patients who showed hematologic relapse received salvage treatment consisting of cytarabine (2 g/m^2, every 12 h, days 1–4), mitoxantrone (12 mg/m^2/day, days 1–4), and etoposide (100 mg/m^2/day, days 5–7) followed by donor lymphocyte infusion (1 × 10^8/kg of recipient) or second HCT from an alternative donor, if possible.

Definitions

Patients were defined as high-risk ALL if they met at least one of the following criteria at diagnosis: (1) older age (≥40 years); (2) high leukocyte counts (≥30 × 10^9/L); (3) poor-risk cytogenetics (*KMT2A* rearrangements, hypodiploidy, complex karyotype [≥5 chromosomal abnormalities]); (4) failure to achieve complete remission (CR) after the first chemotherapy cycle but entering CR after the second cycle (defined as delayed CR). CR was defined as <5% leukemic blasts in the bone marrow, together with an absolute neutrophil count of ≥1.0 × 10^9/L and a platelet count of ≥100 × 10^9/L. GVHD was diagnosed and graded using the previously published criteria [19, 20].

Anchored multiplex PCR (AMP)-based targeted next-generation sequencing (NGS)

We screened Ph-like ALL by AMP-based targeted NGS (Archer® FusionPlex® ALL Kit, ArcherDX, Boulder, CO), which can detect various fusions, mutations, and expression levels in 81 key genes associated with ALL [21]. First, reverse transcription using random primers was performed for synthesis of cDNA, and followed by end repair and adenylation steps. The cleanup of cDNA using Agencourt® AMPure® XP beads and ligation of molecular barcode (MBC) adapters and universal primer sites were performed. The MBC adapter-attached cDNA was amplified by the gene specific primer 1 (GSP1) and primer complementary to universal primer site, and the second PCR using GSP2 was performed. The libraries were quantitated using KAPA Universal Library Quantification Kit (Kapa Biosystems, Woburn, MA), normalized and loaded to NextSeq (Illumina, San Diego, CA) according to manufacturer's instruction. Data were analyzed by the Archer® Analysis version 5.1.7 (ArcherDX). Normalized RNA expression values were calculated by dividing the unique RNA reads for each GSP2 by the arithmetic mean of the unique RNA

reads for all control GSP2s included in the panel. Relative RNA expression values were reported in RNA_expression_visualization.tsv and visualized using heatmaps. Each heatmap showed samples in columns and binned normalized per GSP2 RNA expression values (0–9) in rows.

Cytogenetic analysis and fluorescence in situ hybridization (FISH)

Cytogenetic G-banding analysis was carried out and detected abnormalities were classified according to the 2016 International System for Human Cytogenetic Nomenclature guidelines [22]. FISH was performed with appropriate probes (BCR-ABL1 dual fusion probe, PDGFRB break-apart probe, PDGFRA break-apart probe, JAK2 break-apart probe, IGH break-apart probe, and P2RY8 deletion probe) according to the manufacturer's recommendations (Cytocell, Cambridge, UK).

Reverse transcription PCR (RT-PCR)

To confirm fusion genes detected by AMP-based NGS, multiplex RT-PCR, RT-PCR and FISH were performed. First, we designed two multiplex RT-PCR primers that simultaneously screened 4 and 3 fusion transcripts, respectively; (1) ETV6-ABL1, NUP214-ABL1, EBF1-PDGFRB, P2RY8-CRLF2 and (2) EBF1-JAK2, ETV6-JAK2, BCR-JAK2. The ABL1 gene was used as internal control. Multiplex RT-PCR was conducted using CFX96 (Bio-Rad, Hercules, CA). Next, we validated the fusion transcripts by RT-PCR using previously described in other studies and designed flanking primer by Primer3 (http://bioinfo.ut.ee/primer3-0.4.0/) [9]. The primer sequences used for RT-PCR are provided in supplementary Table S1. Amplification conditions were as follows; initial denaturation at 95 °C for 5 min, 25 PCR cycles, denaturation at 95 °C for 30 s, annealing at 58 °C for 30 s, extension at 72 °C for 90 s and hold at 4 °C.

Measurement of CRLF2 expression

As described in the previous report [8], the CRLF2 gene expression was measured by quantitative RT-PCR (qRT-PCR) using TaqMan® Gene Expression Assays Hs00913509_s1 (Applied Biosystems, Foster City, CA), and the expression of reference gene GUSB as an internal control was measured using TaqMan® Gene Expression Assays Hs00939627_m1 (Applied Biosystems). The 4 μg cDNA of each sample was tested on the 7500 Real Time PCR System instrument (Applied Biosystems). The PCR amplification condition was as follows: 10 min at 95 °C, 50 cycles of 15 s at 95 °C and 1 min at 60 °C. The relative

expression levels were estimated using the $2^{-\Delta\Delta Ct}$ method [23] and were compared to the expression data from AMP-based NGS.

Sanger sequencing

Identified mutations were confirmed by Sanger sequencing. Primers were designed using Primer 3. After first PCR and clean up, second PCR using BigDye terminator (Thermo Fisher Scientific, Cleveland, OH) was done. The reactions were then sequenced using the capillary electrophoresis sequencer ABI Prism 3130xl Genetic Analyzer (Applied Biosystems).

Statistical analysis

Main end points of this study included CR rate, DFS, overall survival (OS), cumulative incidence of relapse, non-relapse mortality (NRM), and cumulative incidence of GVHD. Patient characteristics were compared by using the Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Survival curves were plotted using the Kaplan–Meier method, and subgroups were compared by log-rank tests. Relapse, NRM, and GVHD were calculated using cumulative incidence estimates to accommodate competing events (death for relapse, relapse for NRM, and both death and relapse for GVHD), and subgroups were compared by Gray test. The effect of allo-HCT was analyzed using the Mantel–Byar method [24]. The prognostic significance of covariates affecting OS and DFS was determined by Cox proportional hazards regression model, considering allo-HCT as a time-dependent covariate. The prognostic significance of covariates affecting cumulative incidences of relapse, NRM, and GVHD was determined using Fine-Gray proportional hazards regression for competing events. Multivariate analyses were performed using variables with P value < 0.10 in prior univariate analyses. Because disease subgroup was the main interest of this study, it was included in all steps of model building. All statistical analyses were performed using 'R' software version 2.15.1 (R Foundation for Statistical Computing, 2012). Statistical significance was set at P value < 0.05.

Results

Baseline characteristics and responses to chemotherapy

Of the 344 evaluable patients with BCP-ALL, 57 (16.6%) had Ph-like ALL, 197 (57.3%) had Ph-positive ALL, and 90 (26.1%; 63 standard-risk cytogenetics, 27 poor-risk

Table 1 Baseline and transplant characteristics according to disease subgroup.

	Ph-like (n = 57)	B-other, SR (n = 63)	B-other, PR[a] (n = 27)	P
Age, median (range), years	36 (18–74)	34 (16–62)	41 (17–65)	0.156
<40, n (%)	33 (57.9)	35 (55.6)	12 (44.4)	0.501
≥40, n (%)	24 (42.1)	28 (44.4)	15 (55.6)	
Sex				
Male, n (%)	28 (49.1)	33 (52.4)	15 (55.6)	0.865
Female, n (%)	29 (50.9)	30 (47.6)	12 (44.4)	
Leukocyte count, median (range), ×10⁹/L	12.9 (0.6–124.3)	8.1 (1.1–454.0)	72.1 (1.5–483.3)	0.006
<30, n (%)	40 (70.2)	52 (82.5)	13 (48.1)	0.005
≥30, n (%)	17 (29.8)	11 (17.5)	14 (51.9)	
Platelet count, median (range), ×10⁹/L	67.0 (9.0–276.0)	48.0 (9.0–395.0)	48.0 (5.0–169.0)	0.277
Extramedullary involvement, n (%)	22 (39.3)	34 (54.0)	8 (29.6)	0.065
Year of treatment, n (%)				
2008–2012	13 (22.8)	35 (55.6)	16 (59.3)	<0.001
2013–2016	44 (77.2)	28 (44.4)	11 (40.7)	
CR, n (%)	55 (96.5)	58 (92.1)	22 (81.5)	0.213
CR after the first cycle, n (%)	47 (82.5)	55 (87.3)	19 (70.4)	
Delayed CR[b], n (%)	8 (14.0)	3 (4.8)	3 (11.1)	
High-risk subgroup, n (%)	31 (54.4)	38 (60.3)	27 (100)	<0.001
Allogeneic HCT in CR, n (%)	50 (87.7)	45 (71.4)	19 (70.4)	0.055
Donor source, n (%)				
MSD	26 (52.0)	15 (33.3)	6 (31.5)	0.079
MUD	6 (12.0)	13 (28.9)	4 (21.1)	
1-MMUD	6 (12.0)	9 (20.0)	7 (36.8)	
CB	12 (24.0)	8 (17.8)	2 (10.5)	
Conditioning intensity, n (%)				
Myeloablative	41 (82.0)	36 (80.0)	12 (63.2)	0.025
Reduced-intensity	9 (18.0)	9 (20.0)	7 (36.8)	
Time to HCT[c], median (range), mo	5.4 (3.6–8.2)	5.5 (3.8–7.9)	5.2 (3.5–8.9)	0.685

Ph Philadelphia chromosome, *SR* standard-risk cytogenetics, *PR* poor-risk cytogenetics (*KMT2A* rearrangements, hypodiploidy, and complex karyotype [≥5 chromosomal abnormalities]), *CR* complete remission, *HCT* hematopoietic cell transplantation, *MSD* matched sibling donor, *MUD* matched unrelated donor, *1-MMUD* 1-allele-mismatched unrelated donor, *CB* cord blood.

[a]Poor-risk cytogenetics was defined as *KMT2A* rearrangements, hypodiploidy, and complex karyotype (≥5 chromosomal abnormalities).

[b]Delayed CR was defined as failure to achieve CR after the first chemotherapy cycle but entering CR after the second cycle.

[c]Time to HCT was defined as time interval from diagnosis to transplantation.

cytogenetics) had B-other ALL (Fig. 1). Further analyses of clinical characteristics and outcomes were restricted to 147 patients with Ph-negative BCP-ALL. The baseline characteristics of patients are listed in Table 1. Median patient age was 38 years (range, 16–74 years). Compared with B-other poor-risk ALL, patients with Ph-like ALL had a lower leukocyte counts at diagnosis, a lower percentage of high-risk subgroup, and were treated more recently. The overall CR rates were 96.5% for Ph-like ALL, 92.1% for B-other

standard-risk ALL, and 81.5% for B-other poor-risk ALL. The actual allo-HCT proceeding rates in CR were 87.7% for Ph-like ALL, 71.4% for B-other standard-risk ALL, and 70.4% for B-other poor-risk ALL (P = 0.055).

Overall treatment outcomes

Patients received a median of 2 chemotherapy cycles (range, 1–7 cycles; one [n = 4], two [n = 74], three [n = 54], and four or more [n = 15] cycles). One hundred and fourteen (77.6%) of the 147 patients received allo-HCT in CR at a median time of 5.4 months (range, 3.5–8.9 months) from diagnosis. They received a median of 2 chemotherapy cycles (range, 2–4 cycles) before HCT. The reasons for 33 patients not receiving allo-HCT in CR were early death during induction (n = 2), death in CR during consolidation (n = 4), relapse or refractory (n = 20), and no suitable donor (n = 7). After a median follow-up of 57.4 months (range, 8.0–137.0 months), 75 of the 147 patients (35 of 57 Ph-like ALL, 32 of 63 B-other standard-risk ALL, 8 of 27 B-other poor-risk ALL) are alive, and 71 of the 75 patients remained in persistent CR. At the time of analysis, 72 patients had died; 41 died of progressive leukemia and the remaining 31 died of causes other than leukemic relapse (25 HCT-related complications and 6 chemotherapy-related complications). Forty-two patients relapsed at a median CR duration of 5.0 months (range, 1.0–34.6 months). Cumulative incidences of relapse and NRM at 5 years were 21.4% and 21.5% for Ph-like ALL, 32.2% and 19.5% for B-other standard-risk ALL, and 40.7% and 23.0% for B-other poor-risk ALL, respectively (P = 0.125 and P = 0.971, respectively). As a result, 5-year DFS of patients with Ph-like ALL was comparable to that of patients with B-other standard-risk ALL (53.6% for Ph-like ALL vs 46.8% for B-other standard-risk ALL), but the difference was significant compared with B-other poor-risk ALL subgroup (25.9%; P = 0.014). Likewise, patients with Ph-like ALL had a higher 5-year OS than B-other poor-risk ALL subgroup (60.6% vs 27.1%; P = 0.008), while no differences were observed compared with B-other standard-risk ALL subgroup (53.1%) (Table 2, Fig. 2).

In multivariate analyses (Table 3), compared with Ph-like ALL, B-other poor-risk ALL was associated with a poorer DFS (HR, 2.10; 95% CI, 1.15–3.84; P = 0.015) and OS (HR, 2.24; 95% CI, 1.18–4.24; P = 0.013), while no significant difference was observed between Ph-like ALL and B-other standard-risk ALL subgroup of patients.

Outcomes of patients receiving allo-HCT in CR

Among 114 patients receiving allo-HCT in CR (50 Ph-like ALL, 45 B-other standard-risk ALL, 19 B-other poor-risk

Table 2 Overall treatment outcomes: univariate analysis.

	Ph-like	B-other, SR	B-other, PR	P
All patients (n = 147)				
No. of patients	57	63	27	
Cumulative incidence of relapse at 5 years, % (95% CI)	21.4 (11.7–32.9)	32.2 (20.9–44.0)	40.7 (21.9–58.8)	0.125
Cumulative incidence of NRM at 5 years, % (95% CI)	21.5 (11.8–33.1)	19.5 (10.6–30.3)	23.0 (9.0–40.9)	0.971
DFS rate at 5 years, % (95% CI)	53.6 (39.7–65.6)	46.8 (34.0–58.6)	25.9 (11.5–43.1)	0.014
OS rate at 5 years, % (95% CI)	60.6 (46.5–72.0)	53.1 (40.0–64.6)	27.1 (12.0–44.7)	0.008
Transplants in CR (n = 114)				
No. of patients	50	45	19	
Cumulative incidence of aGVHD at 100 days, % (95% CI)	54.1 (39.1–66.9)	64.4 (48.3–76.7)	47.4 (23.6–67.9)	0.279
Cumulative incidence of cGVHD at 5 years, % (95% CI)	50.6 (35.3–64.1)	46.7 (31.5–60.5)	47.0 (21.0–69.3)	0.871
Cumulative incidence of relapse at 5 years, % (95% CI)	18.1 (8.8–29.9)	17.8 (8.2–30.3)	36.8 (15.8–58.2)	0.117
Cumulative incidence of NRM at 5 years, % (95% CI)	22.3 (11.8–34.8)	18.0 (8.3–30.7)	26.3 (9.0–47.7)	0.818
DFS rate at 5 years, % (95% CI)	59.6 (44.6–71.8)	64.2 (48.3–76.3)	36.8 (16.5–57.5)	0.042
OS rate at 5 years, % (95% CI)	65.6 (50.5–77.0)	68.7 (52.9–80.1)	36.8 (16.5–57.5)	0.024

Ph Philadelphia chromosome, *SR* standard-risk cytogenetics, *PR* poor-risk cytogenetics, *CI* confidence interval, *NRM* non-relapse mortality, *DFS* disease-free survival, *OS* overall survival, *CR* complete remission, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic graft-versus-host disease.

ALL), cumulative incidence of grade II-IV acute GVHD at 100 days for Ph-like ALL, B-other standard-risk ALL, and B-other poor-risk ALL was 54.1%, 64.4%, and 47.4%, respectively. Cumulative incidence of chronic GVHD at 5 years was 50.6% for Ph-like ALL, 46.7% for B-other standard-risk ALL, and 47.0% for B-other poor-risk ALL, respectively. Twenty-four patients relapsed at a median of 9.2 months (range, 1.5–29.1 months) after transplantation. Cumulative incidence of relapse at 5 years was 18.1% for Ph-like ALL, 17.8% for B-other standard-risk ALL, and 36.8% for B-other poor-risk ALL, respectively. Totally, 25 patients died of NRM at a median of 8.5 months (range, 2.0-60.4 months) after transplantation. Five-year incidence of NRM was 22.3% for Ph-like ALL, 18.0% for B-other standard-risk ALL, and 26.3% for B-other poor-risk ALL, respectively. DFS and OS rates at 5 years were 59.6% and 65.6% for Ph-like ALL, 64.2% and 68.7% for B-other standard-risk ALL, and 36.8% and 36.8% for B-other poor-risk ALL, respectively ($P = 0.042$ and $P = 0.024$, respectively) (Table 2). Compared with Ph-like ALL, multivariate analysis showed that B-other poor-risk ALL was associated with a poorer DFS (HR, 2.13; 95% CI, 1.01–4.54; $P = 0.049$), while no difference was observed between Ph-like ALL and B-other standard-risk ALL subgroup of patients. Similarly, B-other poor-risk ALL was related to a poorer OS (HR, 2.32; 95% CI, 1.06-5.08; $P = 0.034$) than Ph-like ALL (Table 3).

Outcomes of patients not including in the analysis

As shown in Fig. 1, 30 patients who did not receive frontline chemotherapy and 65 patients who received frontline chemotherapy but had suboptimal RNA were excluded from this study. In the latter 65 patients (median age, 38 years [range, 17–64 years]), 56 (86.2%) achieved CR. They received a median of 3 chemotherapy cycles (range, 1–7 cycles). Forty-six (70.8%) of the 65 patients received allo-HCT in CR at a median time of 5.7 months (range, 2.4–8.6 months) from diagnosis. To date, 24 patients are alive in persistent CR and 41 patients had died (29 progressive leukemia, 9 HCT-related complications, and 3 chemotherapy-related complications). Twenty-seven patients relapsed at a median CR duration of 7.1 months (range, 1.0-87.6 months). Cumulative incidences of relapse and NRM at 5 years were 42.9% and 29.1%, respectively. DFS and OS rates at 5 years were 28.0% and 39.2%, respectively.

Genetic characteristics and outcomes of Ph-like ALL subgroup analysis

All identified fusions and mutations are summarized in Fig. 3. Of the 57 patients with Ph-like ALL, we detected fusion transcripts in 24 patients (42.1%). Thirteen patients had *CRLF* rearrangements, including seven with *P2RY8-*
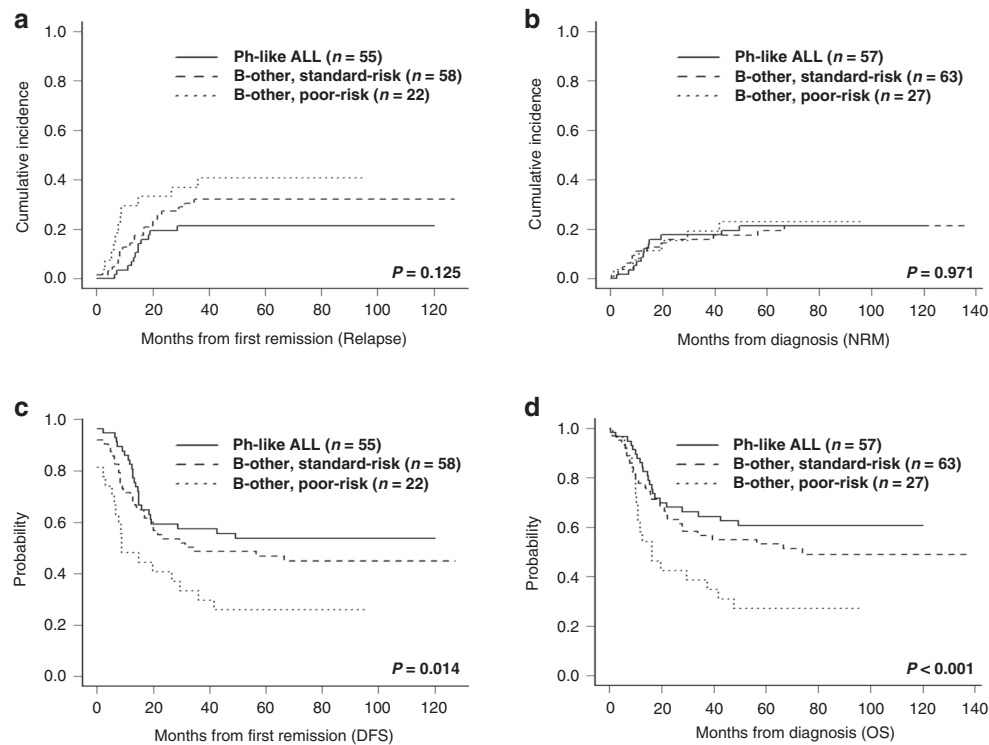
Fig. 2 Outcomes of all patients according to disease subtype. a Cumulative incidence of relapse. **b** Cumulative incidence of non-relapse mortality. **c** Disease-free survival. **d** Overall survival.

CRLF2, four with *IGH-CRLF2*, one with *CLDN7-CRLF2*, and one with *HFM1-CRLF2*. Among them, six patients had concomitant *JAK2* or *CRLF2* mutations; two had mutations in *CRLF2* and four had mutations in *JAK2* and *CRLF2*. Seven patients had *JAK2* rearrangements and their fusion partners were *PAX5* ($n = 2$), *BICD2* ($n = 1$), *SMU1* ($n = 1$), *ROCK1* ($n = 1$), *ZCCHC7* ($n = 1$), and *ZFP14* ($n = 1$). ABL-class rearrangements were found in five patients, including *NUP214-ABL1* ($n = 2$), *EBF1-PDGFRB* ($n = 2$), and *RCSD1-ABL2* ($n = 1$) (Supplementary Fig. S2). Sequence mutations in genes activating JAK-STAT signaling were identified in 15 patients without *CRLF* rearrangements or other kinase fusions, including in *IL7R* ($n = 4$), *FLT3* ($n = 7$), *TYK2* ($n = 2$), *JAK2* ($n = 1$), and *EPOR* ($n = 1$). Seventeen patients had alterations in the RAS pathway only, including sequence mutations in *NRAS* ($n = 7$), *KRAS* ($n = 5$), *PTPN11* ($n = 4$), *NRAS/KRAS/PTPN11* ($n = 1$). Here, we classified patients with Ph-like ALL into 5 subgroups; (1) *CRLF2* abnormalities ($n = 13$, 22.8%), (2) *JAK2* rearrangements ($n = 7$, 12.3%), (3) ABL-class rearrangements ($n = 5$, 8.8%), (4) other JAK-STAT pathway mutations ($n = 15$, 26.3%), and (5) RAS pathway mutations ($n = 17$, 29.8%). Within the Ph-like ALL subgroup, patients with *CRLF2* abnormalities or ABL-class rearrangements had an inferior OS than patients with other genetic alterations. In contrast, patients with isolated RAS pathway mutations had a lower cumulative incidence of relapse and

better OS (Fig. 4). We also found that *IKZF1* deletions were more common in patients with Ph-like ALL than in those with B-other ALL lacking known recurrent genetic abnormalities (21 of 57 [36.8%] vs 4 of 40 [10.0%]; $P = 0.004$). Within the Ph-like ALL subgroup, *IKZF1* deletions were not significantly associated with relapse or OS (Supplementary Fig. S3).

Discussion

Although gene expression profiling is the standard for diagnosis of Ph-like ALL, this tool is not widely available in routine clinical practice and requires time to generate results. Therefore, various approaches and methods have been developed to identify these patients in a more practical fashion. The Children's Oncology Group developed a diagnostic algorithm for identifying patients with Ph-like ALL [25]. They used a qRT-PCR-based low density array platform as a screening tool and performed additional downstream tests (e.g., FISH, RT-PCR, RNA sequencing, etc.) in dedicated reference laboratories for the identification of specific genetic alterations. While this approach is now being performed in clinical trials, timely completion of all necessary testing by the end of induction can be challenging in some cases. In addition to the above tiered approach, recent advances in NGS technologies have led to

Table 3 Multivariate analysis for relapse, NRM, DFS, and OS.

	Relapse		NRM		DFS		OS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All patients								
Disease subgroup								
Ph-like	1		1		1		1	
B-other, SR	1.27 (0.53–3.07)	0.590	1.12 (0.47–2.65)	0.800	1.31 (0.77–2.22)	0.324	1.35 (0.76–2.39)	0.300
B-other, PR	2.49 (0.88–7.01)	0.083	1.21 (0.43–3.39)	0.710	2.10 (1.15–3.84)	0.015	2.24 (1.18–4.24)	0.013
Age								
<40 years	1		1		1		1	
≥40 years	1.50 (0.71–3.18)	0.290	1.00 (0.48–2.09)	1.000	1.48 (0.95–2.31)	0.083	1.66 (1.04–2.67)	0.034
Leukocyte count, ×10⁹/L								
<30	1		1		1		1	
≥30	1.02 (0.40–2.54)	0.970	1.05 (0.47–2.33)	0.910	1.30 (0.80–2.11)	0.291	1.24 (0.74–2.08)	0.410
Year of treatment, *n* (%)								
2008–2012	1		1		1		1	
2013–2016	0.98 (0.45–2.15)	0.960	1.46 (0.67–3.18)	0.340	1.01 (0.64–1.59)	0.977	0.98 (0.60–1.59)	0.930
Transplants in CR								
Disease subgroup								
Ph-like	1		1		1		1	
B-other, SR	0.98 (0.38–2.53)	0.970	0.88 (0.35–2.22)	0.790	0.93 (0.47–1.82)	0.829	0.98 (0.48–2.01)	0.964
B-other, PR	3.04 (1.02–9.06)	0.046	1.11 (0.38–3.30)	0.840	2.13 (1.01–4.54)	0.049	2.32 (1.06–5.08)	0.034
Age								
<40 years	1		1		1		1	
≥40 years	1.82 (0.80–4.15)	0.15	1.17 (0.49–2.80)	0.720	1.63 (0.91–2.91)	0.097	1.53 (0.83–2.80)	0.169
Leukocyte count, ×10⁹/L								
<30	1		1		1		1	
≥30	0.67 (0.22–2.04)	0.480	1.40 (0.59–3.30)	0.440	0.98 (0.51–1.91)	0.966	1.02 (0.51–2.04)	0.945
Year of treatment, *n* (%)								
2008–2012	1		1		1		1	
2013–2016	1.30 (0.54–3.07)	0.560	1.05 (0.43–2.53)	0.910	1.25 (0.69–2.30)	0.458	1.07 (0.57–2.01)	0.816
Donor source								
MSD	1		1		1		1	
Others[a]	0.75 (0.31–1.84)	0.540	1.05 (0.43–2.53)	0.910	1.02 (0.56–1.84)	0.949	1.04 (0.56–1.94)	0.890

NRM non-relapse mortality, *DFS* disease-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *SR* standard-risk cytogenetics, *PR* poor-risk cytogenetics, *CR* complete remission, *MSD* matched sibling donor.

[a]Others included matched unrelated donor, 1-allele-mismatched unrelated donor, and cord blood.

development of several commercially-available platforms capable of highly sensitive detection of leukemia-associated fusions and mutations. One practical option is the capture-based sequencing for the common genetic alterations in NGS panels, as was done in our study. In our study, the frequency of Ph-like ALL was 16.6% in 344 evaluable adults with newly diagnosed BCP-ALL who received a uniform chemotherapy and had suitable material for genomic analysis. Recent studies have identified the Ph-like ALL subgroup in 13–33% of adult patients [12–16]. These variations are probably caused by differences in the race and ethnicity of the studied population. In a study from the MD

Anderson Cancer Center, 33% of adult patients had Ph-like ALL, and the frequency of Ph-like ALL was particularly high in Hispanic patients [14]. This could be related to inherited variants in the *GATA3* gene [26]. In addition, various methods without standardization to identify Ph-like ALL may have led to these inconsistent results.

In this study, to better evaluate the prognosis of Ph-like ALL, further outcome analyses were restricted to 147 patients with Ph-negative BCP-ALL (57 Ph-like ALL vs 63 B-other standard-risk ALL vs 27 B-other poor-risk ALL). Our data showed that the overall CR rates were 96.5% for Ph-like ALL, 92.1% for B-other standard-risk ALL, and
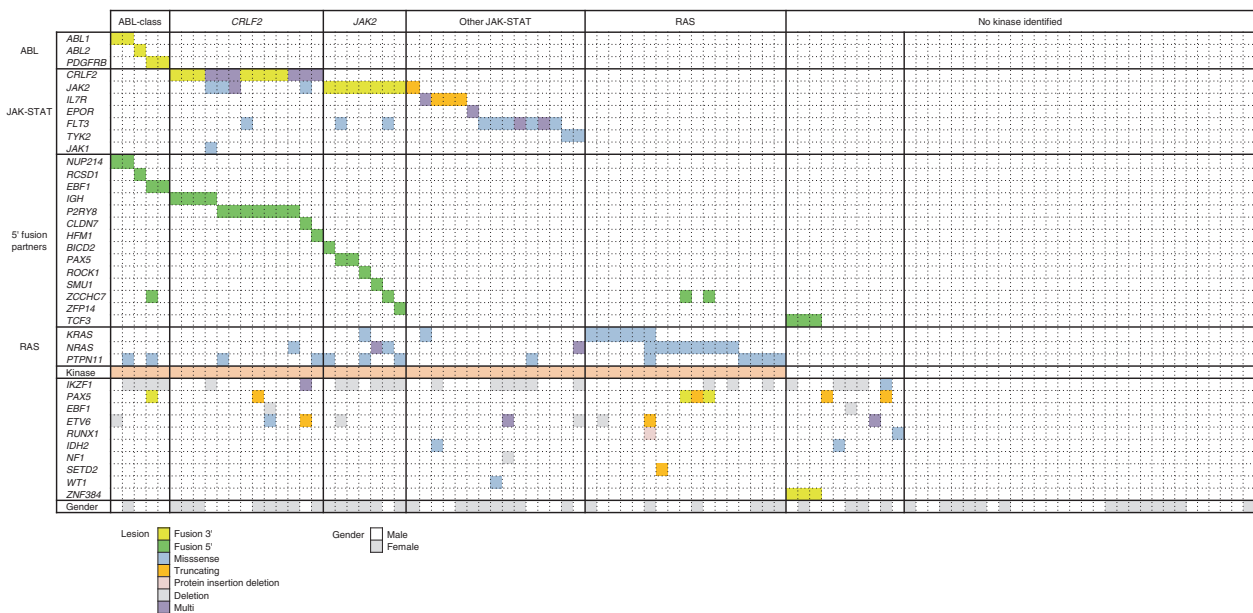
Fig. 3 **Genetic alterations identified in patients.** Data are shown for 57 patients with Ph-like ALL divided into patients with ABL-class fusions (*ABL1*, *ABL2*, and *PDGFRB*), *CRLF2* rearrangements, *JAK2* rearrangements, other JAK–STAT–activating mutations (*JAK2*, *IL7R*, *EPOR*, *FLT3*, *TYK2* and *JAK1*), alterations in the RAS pathway (*KRAS*, *NRAS*, and *PTPN11*), and 40 patients with no kinase alteration.
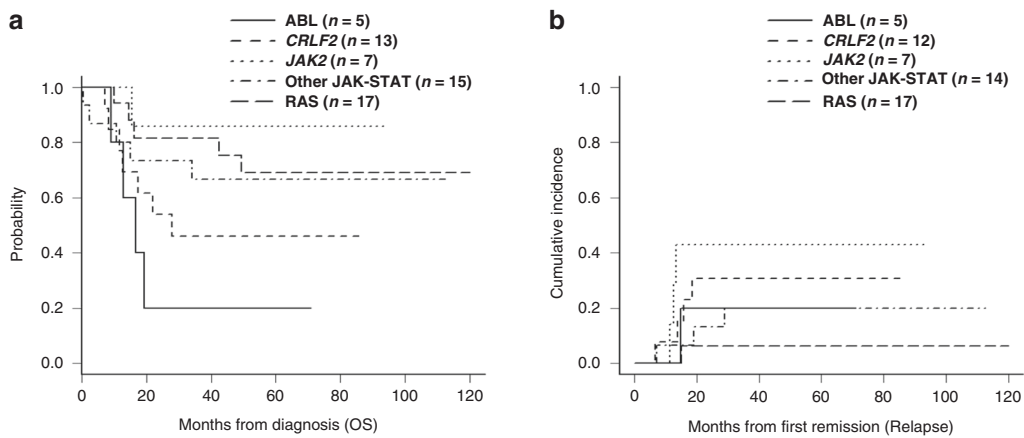

Fig. 4 **Outcomes between different genetic subgroups in Ph-like ALL. a** Overall survival. **b** Cumulative incidence of relapse.

81.5% for B-other poor-risk ALL. Patients with Ph-like ALL had a better DFS and OS than those with B-other poor-risk ALL, while no significant difference was observed between Ph-like ALL and B-other standard-risk ALL subgroups. The actual allo-HCT proceeding rates in CR were 87.7% for Ph-like ALL, 71.4% for B-other standard-risk ALL, and 70.4% for B-other poor-risk ALL.

To date, no published trials address the role of allo-HCT specifically in adults with Ph-like ALL. In this study, patients with a donor proceeded to allo-HCT as a main post-remission therapy. Unexpectedly, patients with Ph-like ALL showed better outcomes than those with B-other poor-risk ALL, and no significant differences were found compared with B-other standard-risk ALL. However, this study was

not specifically designed to define the power of allo-HCT in this genetic subgroup. Indeed, our results are limited to assess the role of allo-HCT by the fact that the majority of patients underwent allo-HCT in CR. Additionally, assignments to the allo-HCT group are primarily based on the availability of suitable donors, so patient selection bias and difference in the time interval from diagnosis to transplantation may affect study endpoints. Nevertheless, our findings are partly supported by one pediatric study from the St. Jude Children's Research Hospital [27]. They demonstrated that the adverse prognosis of Ph-like ALL can be improved by MRD-based risk-directed therapy, including allo-HCT for high-risk subgroup. Taken together, our findings suggest that allo-HCT-based post-remission therapy may have

contributed to non-inferior outcomes of adults with Ph-like ALL. These findings should be further evaluated by well-designed prospective trials.

Our study has several limitations of a retrospective analysis that could have influenced on data interpretation. It should be considered that our chemotherapy regimen differed from other studies. In combination with mitoxantrone instead of methotrexate, we used a higher dose of cytarabine than the original hyper-CVAD-based therapy every even cycle [28]. In addition, we could not further demonstrate the effect of conditioning intensity or each donor-graft source on HCT outcomes due to sample size limitations. Another major limitation of our study is the lack of MRD assessment in the studied population. During the study period, we were unable to address the impact of MRD status according to disease subgroup because MRD data were available for only Ph-positive ALL. In the chemotherapy setting, most studies have demonstrated that patients with Ph-like ALL have less frequent MRD-negative CR and poorer outcomes compared with non-Ph-like ALL subgroup [5, 9, 12–15]. Interestingly, the MD Anderson Cancer Center group reported that post-induction MRD negativity had no significant impact on long-term OS of adults with Ph-like ALL [14]. In children, one study showed non-inferior outcomes in a cohort of patients with Ph-like ALL using an MRD-directed intensive therapy [27]. However, another pediatric study from an Australian group reported poor outcomes despite a risk-adjusted treatment approach [29]. Further studies to determine the prognostic role of MRD during whole treatment course and the intensification of treatment based on MRD response need to be explored more in patients with Ph-like ALL.

Within the Ph-like ALL subgroup, specific genetic alterations probably have different impacts on treatment outcomes. A recently published study in adult patients showed a trend toward inferior survival in patients harboring rearrangements of *CRLF2* or *JAK2/EPOR* than patients with other alterations [15]. Another study of adult patients also showed that *CRLF* overexpression was associated with poor outcomes with 5-year OS of less than 20% [14]. In contrast, among children and young adults, Roberts et al. reported favorable outcomes with 5-year event-free survival of 85.7% in patients with isolated RAS pathway alterations [9]. Within the limitation of sample size in our Ph-like ALL subgroup, patients with *CRLF2* abnormalities or ABL-class rearrangements had an inferior OS, while patients with isolated RAS pathway mutations had a lower cumulative incidence of relapse and better OS. Notably, compared with Western reports, our patients had lower frequencies of *CRLF2* abnormalities or ABL-class rearrangements but a higher proportion of isolated RAS mutations. Therefore, these inconsistent findings are probably caused by racial and ethnic differences in the studied population. Also,

differences in studied sample size and methods for identifying the Ph-like ALL genetic signature and genomic characterization should be considered.

In summary, our data showed racial and ethnic differences in the frequency of Ph-like ALL and the spectrum of Ph-like genetic alterations. Allo-HCT-based post-remission therapy may have contributed to non-inferior outcomes of adults with Ph-like ALL. Our findings should be further evaluated with thorough MRD monitoring to address the necessity of allo-HCT in this genetic subgroup. In addition, given the anecdotal responsiveness to TKI therapy in a subgroup of patients with Ph-like ALL and the success of antibody-based immunotherapy in the treatment of BCP-ALL, incorporation of these therapies in the context of allo-HCT needs to be studied as well.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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