## *BCR-ABL* translocation as a favorable prognostic factor in elderly patients with acute lymphoblastic leukemia in the era of potent tyrosine kinase inhibitors

The clinical outcome of acute lymphoblastic leukemia (ALL) depends strongly on the dose-intensity of chemotherapy delivered. The importance of dose-intensity resulted in the establishment of pediatric-inspired regimens for the treatment of fit adults with ALL.[1] ALL patients with the *BCR-ABL* translocation, the so-called Philadelphia chromosome-positive ALL (Ph+ ALL), form a distinct subgroup, accounting for 20-30% of the adult ALL population.[2] Although the *BCR-ABL* translocation is a well-known adverse prognostic factor in ALL, treatment of Ph+ ALL has improved dramatically with the advent of tyrosine kinase inhibitors (TKI) targeting ABL kinase. Imatinib, nilotinib, dasatinib, and ponatinib have all shown promising efficacy in terms of increased complete remission achievement and prolonged relapse-free survival and overall survival in Ph+ ALL.[3-5] Allogeneic stem cell transplantation (ASCT) remains the recommended consolidative treatment for fit Ph+ ALL patients, but recent evidence suggests that newer ABL TKI are capable of long-term disease control without ASCT in certain Ph+ ALL populations.[5,6] Some reports have even suggested the possibility of using these second- and third-generation TKI as the sole consolidation modality without cytotoxic chemotherapy.[5] Epidemiologically, patients over 60 years of age account for a significant proportion of ALL patients. These elderly patients are often unfit for either dose-intensive chemotherapy or ASCT and their clinical outcomes have, therefore, been dismal. The increased incidence of *BCR-ABL* translocation with older age also contributes to the poor prognosis of elderly ALL patients. However, we conjectured that, with the introduction of potent TKI targeting ABL, the *BCR-ABL* translocation might not have a negative prognostic impact in elderly ALL. Considering that many elderly Ph- ALL patients do not tolerate the cytotoxic chemotherapy required for effective tumor control, we supposed that the efficacy of ABL TKI and their combination with low-dose cytotoxic chemotherapy[7] would result in better survival for elderly Ph+ ALL patients compared to their Ph- counterparts. Through our study we confirmed our hypothesis and found that Ph chromosome positivity may actually be a better prognostic factor in elderly patients in the era of potent TKI.

This study was a multicenter, retrospective, longitudinal cohort study of elderly patients (≥60 years) with *de novo* ALL recruited from 13 hospitals in Korea between January 2006 and December 2015. Overall 114 patients were identified and after exclusion of 11 with incomplete data, 103 cases were finally evaluated. Five patients in the Ph+ group did not receive a TKI (1 due to poor oral intake, 1 due to the patient's refusal and 3 for unknown reasons), and they were excluded from the analyses. This study was conducted according to the Declaration of Helsinki and was approved by the institutional review boards of all the participating hospitals. We considered a patient to have Ph+ ALL if the translocation was found by at least one of three techniques: conventional cytogenetics, fluorescence *in situ* hybridization, or quantitative real-time polymerase chain reaction. Differences between groups were assessed using the Student t-test or one-way analysis of variance for continuous variables, and the Pearson chi-square test for categorical variables, as indicated. Complete remission was defined as less than 5% blasts in bone marrow, while relapse was defined by recurrence of a bone marrow blast count above 5% or extramedullary disease after a previously documented complete remission. The overall and relapse-free survival curves were estimated using the Kaplan-Meier method. Overall survival was defined as the time from ALL diagnosis to death, and relapse-free survival as the time from ALL diagnosis to relapse or death. If patients survived without progression, survival was censored on the latest date of follow-up. If the patient underwent ASCT, overall and relapse-free survival were censored at the time of transplantation. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors for relapse-free survival and overall survival. Factors associated with ALL prognosis, including age, white blood cell count at diagnosis, Philadelphia chromosome status, ALL subtype, and induction regimen were included in multivariate analyses. All data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS®Statistics, version 22.0).

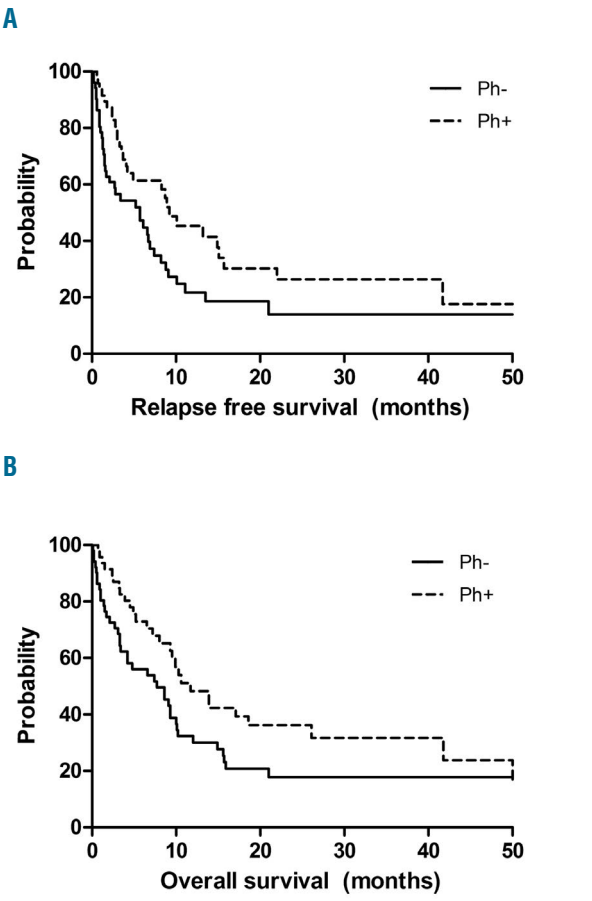


**Figure 1. Survival curves using the Kaplan-Meier method.** (A) Relapse-free survival (*P*=0.031). (B) Overall survival (*P*=0.037).

Of the 98 patients analyzed, 51 (52.0%) had Ph- ALL and 47 (48.0%) had Ph+ ALL. There were no differences between the two groups with regards to age, sex distribution, performance status, and induction regimens (Table 1). Ph+ ALL patients had higher peripheral and bone marrow blast counts at diagnosis. *MLL* rearrangement status was available for 37 (72.5%) of the Ph- ALL patients, and four (10.8%) were positive for the genetic

**Table 1.** Baseline characteristics and treatment of the 98 patients.

| Characteristics | Total | Ph - (N,%) | Ph +, TKI users (N, %) | *P* |
|---|---|---|---|---|
| Total | 98 | 51 (52.0)) | 47 (48.0) | NA |
| Median age, years (range) | 67 (60-86) | 67 (60-86) | 66 (60-75) | 0.150 |
| Sex (male) | 45 (45.9) | 20 (39.2) | 25 (53.2) | 0.165 |
| Performance status | | | | |
| ECOG 0-1 | 31 (31.6) | 15 (29.4) | 16(34.0) | 0.622 |
| ECOG ≥2 | 67 (68.4) | 36 (70.6) | 31 (66.0) | |
| Presentation at diagnosis | | | | |
| Splenomegaly | 34 (34.7) | 18 (35.3) | 16 (34.0) | 1.000 |
| Hepatomegaly | 12 (12.2) | 7 (13.7) | 5 (10.6) | 0.641 |
| Lymphadenopathy | 29 (29.6) | 16 (31.4) | 13 (27.7) | 0.687 |
| Mediastinal mass | 4 (4.1) | 4 (7.8) | 0 | 0.050 |
| CNS involvement | 4 (4.1) | 3 (5.9) | 1 (2.1) | 0.348 |
| Immunophenotype | | | | |
| Pre-B | 74 (75.5) | 34 (66.7) | 40 (85.1) | 0.091 |
| Mature B | 13 (13.3) | 8 (15.7) | 5 (10.6) | |
| T | 9 (9.2) | 8 (15.7) | 1 (2.1) | |
| Mixed | 2 (2.0) | 1 (2.0) | 1 (2.1) | |
| Breakpoint | | | | |
| Major ($p190^{BCR-ABL}$) | 18 | NA | 18 (38.3) | NA |
| Minor ($p210^{BCR-ABL}$) | 25 | NA | 25 (53.2) | NA |
| Undetermined | 4 | NA | 4 (8.5) | NA |
| *MLL* rearrangement | | | | |
| Present | 4 | 4 (7.8) | NA | NA |
| Not present | 34 | 34 (66.7) | NA | NA |
| Undetermined | 13 | 13 (25.5) | NA | NA |
| Laboratory results (mean ± SD) | | | | |
| White blood cell counts ($10^9$/L) | 48.9±33.0 | 35.3±62.9 | 63.6±92.5 | 0.078 |
| Hemoglobin (g/dL) | 9.2±2.5 | 9.5±2.4 | 8.9±2.6 | 0.222 |
| Platelets ($10^9$/L) | 86.9±85.4 | 101.5±93.0 | 71.0±74.1 | 0.077 |
| Lactate dehydrogenase (IU/L) | 1622.3±2094.7 | 1948.2±2716.4 | 1257.6±938.7 | 0.121 |
| Bilirubin (mg/dL) | 0.9±1.0 | 1.0±1.2 | 0.8±0.8 | 0.364 |
| Uric acid (mg/dL) | 5.6±2.6 | 5.7±3.0 | 5.6±2.3 | 0.755 |
| Alkaline phosphatase (IU/L) | 143.8±165.2 | 146.9±159.7 | 140.3±172.8 | 0.847 |
| Peripheral blasts (%) | 38.3±33.0 | 31.4±32.1 | 45.9±32.7 | 0.028 |
| Bone marrow blasts (%) | 73.6±28.0 | 67.1±32.2 | 80.8±20.6 | |
| Induction regimen | | | | 0.015 |
| VPD(L) | 57 (58.2) | 30 (58.8) | 27 (57.4) | 0.490 |
| HyperCVAD | 30 (30.6) | 16 (31.4) | 14 (29.8) | |
| CALGB | 7 (7.1) | 2 (3.9) | 5 (10.6) | |
| Others | 4 (4.1) | 3 (5.9) | 1 (2.1) | |
| Response to induction | | | | |
| Complete remission | 72 (73.5) | 31 (60.8) | 41 (87.2) | 0.003 |
| Induction death | 19 (19.4) | 15 (29.4) | 4 (8.5) | 0.009 |
| TKI | | | | |
| 1st line imatinib | 42 | NA | 42 (89.4) | NA |
| 1st line nilotinib | 5 | NA | 5 (10.6) | NA |
| 1st line dasatinib | 0 | NA | 0 | NA |
| 2nd line TKI use | 10 | NA | 10 (21.3) | NA |
| Switch due to intolerance | 8 | NA | 8 (80.0) | NA |
| Switch due to treatment failure | 2 | NA | 2 (20.0) | NA |
| Treatment outcome | | | | |
| Relapse | 67 (68.4) | 38 (74.5) | 29 (61.7) | 0.173 |
| Death | 68 (69.4) | 40 (78.4) | 28 (59.6) | 0.043 |
| Infection | 33 (48.5) | 24 (60.0) | 9 (32.1) | |
| Disease progression | 21 (30.9) | 9 (22.5) | 12 (42.9) | |
| Bleeding | 3 (4.4) | 2 (5.0) | 1 (3.6) | |
| Unknown/others | 13 (19.1) | 5 (12.5) | 8 (17.0) | |

Ph: Philadelphia chromosome; NA: not applicable; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system; SD: standard deviation; VPD(L): vincristine, prednisolone, daunorubicin ± l-asparaginase; hyperCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone; CALGB: CLAGB 8811 Larson regimen; TKI: tyrosine kinase inhibitor.

aberration. The most common induction regimen used was vincristine, prednisolone, daunorubicine ± l-asparaginase. In the Ph+ group, one patient received TKI monotherapy without a cytoxic chemotherapy backbone. Forty-seven patients were treated with a TKI, of which the most commonly used was imatinib (87.2%). Fifteen patients were given a second-generation TKI: five were given frontline nilotinib while ten switched to second-line dasatinib after imatinib use. The estimated median duration of first-line TKI use was 6 months. Four Ph+ ALL patients subsequently underwent hematopoietic stem cell transplantation after achieving complete remission with induction therapy.

Complete remission was attained by 31 (60.8%) of the patients in the Ph- group and 41 (87.2%) in the Ph+ group ($P$=0.003). The median relapse-free survival was significantly longer in the Ph+ group after induction (5.5 months *versus* 9.2 months for Ph- and Ph+ patients, respectively; $P$=0.031) (Figure 1A). Philadelphia chromosome positivity was recognized as an independent good prognostic factor for relapse-free survival [hazard ratio (HR) 0.528; 95% confidence interval (CI): 0.313-0.890; $P$=0.017] in multivariate analysis. Induction death and induction failure occurred significantly more frequently in the Ph- group, and the most common cause of induction death was infection. During the median follow-up of 33 months, the median overall survival was 7.7 months for the Ph- group compared to 11.7 months for the Ph+ group ($P$=0.037) (Figure 1B). Patients exposed to a second-generation TKI at any point of treatment tended to have a better overall survival than those treated only with a first-generation TKI ($P$=0.09, *data not shown*). In multivariate analysis, Philadelphia chromosome positivity (HR 0.558; 95% CI: 0.333-0.934; $P$=0.026) was recognized as an independent good prognostic factor for overall survival.

Using real world data, this study reports the possible favorable impact of Philadelphia chromosome positivity in elderly ALL patients in the TKI era. Although there are some limitations to this study, including its retrospective nature, heterogeneous treatment regimens and lack of T315I mutation status information for those subjected to a TKI line switch, we observed that Ph+ ALL patients had a higher complete remission rate after induction, longer relapse-free survival and better overall survival. Both univariate and multivariate analyses for relapse-free survival and overall survival indicated that Philadelphia chromosome positivity is an independent good prognostic factor. This result coincides with our assumption that elderly ALL patients who cannot tolerate either dose-intensive chemotherapy or ASCT would get much benefit from TKI when there is an adequate target. Furthermore, these benefits of TKI in elderly patients seem rather promising, to the point of overcoming the aggressive biology of the *BCR-ABL* translocation in ALL.

While it is true that previous studies and clinical trials found an improved prognosis for elderly Ph+ ALL patients in the imatinib era,[8,9] relatively few studies specifically investigated whether TKI can overcome the negative impact of the Philadelphia chromosome on the prognosis of elderly ALL patients by direct comparison. Ribera *et al*. compared two parallel prospective trials, ALLOLD07 and ALLOPH07, showing that, in the era of TKI treatment, older patients with Ph+ ALL do not have a poorer prognosis than those without the Philadelphia chromosome.[10] We went further to validate that elderly Ph+ ALL patients do not just have equivalent clinical outcomes but actually now have a better prognosis than their Ph- ALL counterparts. Compared to the study by Ribera *et al*., our study had (i) more patients, (ii) a larger proportion of Ph+ ALL patients receiving second-generation TKI, and (iii) Ph+ ALL patients who were treated with more intensive cytotoxic chemotherapy than "dexamethasone+vincristine", the backbone cytotoxic chemotherapy used in the ALLOPH07 trial. We assume that these differences resulted in the distinct clinical benefit of TKI in elderly Ph+ ALL patients in our study. A recent study comparing prospective trials from the PETHEMA group supports our finding by reporting better survival for elderly Ph+ ALL patients compared to Ph- ALL patients.[11] Given that ever more Ph+ ALL patients are expected to receive next-generation ABL TKI in the near future, we expect this positive prognostic impact of the *BCR-ABL* translocation in elderly ALL to be validated, if not amplified and solidified in upcoming studies. In fact, recent data concerning dasatinib[12] and ponatinib[7] indicate that next-generation TKI are able to control *BCR-ABL*-translocated acute leukemic cells, even in the absence of an intensive chemotherapy consolidation regimen or ASCT. Further issues for this particular set of patients may include whether TKI use is associated with better quality of life, and which TKI and for how long it should be administered.

Elderly ALL patients still represent an important area of need. Recently, combinations of TKI with minimally-toxic agents, including T-cell therapy[13] and CDK inhibitors,[14] to overcome the shortcomings of TKI therapy have yielded positive results. Moreover, with the advent of studies based on next-generation sequencing, diverse oncogenic drivers are being recognized followed by subsequent development of many small molecules targeting these oncogenic drivers in ALL.[15] Our study points out the importance of developing effective targeted agents in ALL, and that the population who would benefit most from these targeted agents consists of elderly ALL patients who cannot tolerate intensive chemotherapy and ASCT.

*Ja Min Byun,[1,2,3] Youngil Koh,[1] Dong-Yeop Shin,[1] Inho Kim,[1] Sung-Soo Yoon,[1] Jeong-Ok Lee,[2] Soo-Mee Bang,[2] Ki Hwan Kim,[3] Sung-Hoon Jung,[4] Won Sik Lee,[5] Yong Park,[6] Jun Ho Jang,[7] Jae Joon Han,[8] Ho-Young Yhim,[9] Dae Sik Kim,[10] Yoo Jin Lee,[11] Hyewon Lee,[12] Yun-Suk Choi[13] and Seok Lee[14] on behalf of the Korean Adult ALL Working Party, Korean Society of Hematology*

*[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital; [2]Department of Internal Medicine, Seoul National University Bundang Hospital; [3]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center; [4]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital; [5]Department of Internal Medicine, Inje University Busan Paik Hospital; [6]Department of Internal Medicine, Korea University School of Medicine Anam Hospital; [7]Divison of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine; [8]Department of Internal Medicine, School of Medicine, Kyung Hee University; [9]Division of Hematology-Oncology, Department of Internal Medicine, Chonbuk National University Hospital; [10]Department of Internal Medicine, Korea University School of Medicine, Seoul; [11]Department of Hematology-Oncology, Kyungpook National University Hospital; [12]Hematologic-Oncology Clinic, Center for Specific Organs Cancer, National Cancer Center, Goyang; [13]Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine and [14]Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea*

*Funding: this study was supported by grant N. 0320160410 from*

*the Seoul National University Hospital Research Fund.*

*The abstract of this manuscript has been submitted to the American Association for Cancer Research (AACR) Annual Meeting 2017.*

*Correspondence: go01@snu.ac.kr*
*doi:10.3324/haematol.2016.159988*

*Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.*

## References

1. DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. Leukemia. 2015;29(3):526-534.
2. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189-3197.
3. Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica. 2015;100(5):653-661.
4. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746-756.
5. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2011;118(25):6521-6528.
6. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol. 2015;16(15):1547-1555.
7. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015; 125(24):3711-3719.
8. Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer. 2007;109(10):2068-2076.
9. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood. 2007;109(9):3676-3678.
10. Ribera JM, Garcia O, Fernandez-Abellan P, et al. Lack of negative impact of Philadelphia chromosome in older patients with acute lymphoblastic leukaemia in the thyrosine kinase inhibitor era: comparison of two prospective parallel protocols. Br J Haematol. 2012; 159(4):485-488.
11. Ribera JM, Garcia O, Oriol A, et al. Feasibility and results of subtype-oriented protocols in older adults and fit elderly patients with acute lymphoblastic leukemia: results of three prospective parallel trials from the PETHEMA group. Leuk Res. 2016;41(2):12-20.
12. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015;121(23):4158-4164.
13. Comoli P, Basso S, Riva G, et al. BCR-ABL-specific T-cell therapy in Ph+ ALL patients on tyrosine-kinase inhibitors. Blood. 2017; 129(5):582-586.
14. Nemoto A, Saida S, Kato I, et al. Specific antileukemia activity of PD0332991, a CDK4/6 inhibitor, against Philadelphia chromosome positive lymphoid leukemia. Mol Cancer Ther. 2016;15(1):94-105.
15. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. Cancer. 2015;121(15):2517-2528.