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Letter
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High-risk Combinations of Additional Chromosomal Abnormalities in Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia: JALSG Ph+ALL TKI-SCT Study

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Additional chromosomal abnormalities (ACAs) are found in 60%–70% of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) cases. Although some high-risk chromosomal and genetic abnormalities have recently been reported,[1,2] they have not been established as risk factors.[3] The purpose of this study was to explore the prognostic importance of ACAs for Ph+ALL.

This study combined 3 Japan Adult Leukemia Study Group (JALSG) prospective studies in the era of tyrosine kinase inhibitors (TKIs): 77 registered in the Ph+ALL202 study, 55 registered in the Ph+ALL208 study, and 74 registered in the Ph+ALL213 study. The detailed treatment schedules for each study are described elsewhere.[4-6] The Ph+ALL202 study was the first JALSG study using imatinib for Ph+ALL. In the Ph+ALL208 study, imatinib was also used as a TKI, but the emphasis was on the combination of chemotherapy and imatinib, and the duration of imatinib monotherapy was shorter compared with the Ph+ALL202 study. In the Ph+ALL213 study, dasatinib was used instead of imatinib, and the induction phase was separated into 2 steps (Supplemental Methods). In this study, we used chromosomal data reviewed in the final analysis of each study. A complex karyotype was defined by the presence of at least 3 abnormalities (ie, t[9;22] and 2 or more additional aberrations) as previously described.[7-9]

We analyzed data from 206 de novo adult Ph+ALL patients (Suppl. Table S1). The median age at diagnosis was 45 years, white blood cell count at diagnosis was 23,510/μL, and the TKI of initial treatment was imatinib in 132 patients (64.1%) and dasatinib in 74 patients (35.9%). An ACA was identified in 63.6% of all patients; the most common structural chromosomal abnormality was +der(22)t(9;22) (32.8% of patients with an ACA). A complex karyotype was observed in 48.1% of patients with an ACA. Of 152 evaluable patients, 121 (79.6%) achieved molecular complete remission (CR) at 3 months. Allogeneic stem cell transplantation (allo-SCT) in the first CR (CR1) was performed in 138 (67.0%) of 206 patients.

Regarding the overlap of ACAs, the pairwise analysis showed significant cooccurrence of +der(22)t(9;22) with both abnormal 9p and a complex karyotype (Figure 1; Suppl. Figure S1). Among 43 patients with +der(22)t(9;22), 67.4% also had a complex karyotype. On the contrary, +der(22)t(9;22) was observed in 46.0% of 63 patients with a complex karyotype.

At 5 years, the overall survival (OS) was 58.8% (95% confidence interval [CI], 51.4%-65.4%) in all 206 patients. OS was significantly higher in patients treated with dasatinib compared with those treated with imatinib (dasatinib: 74.2% [95%

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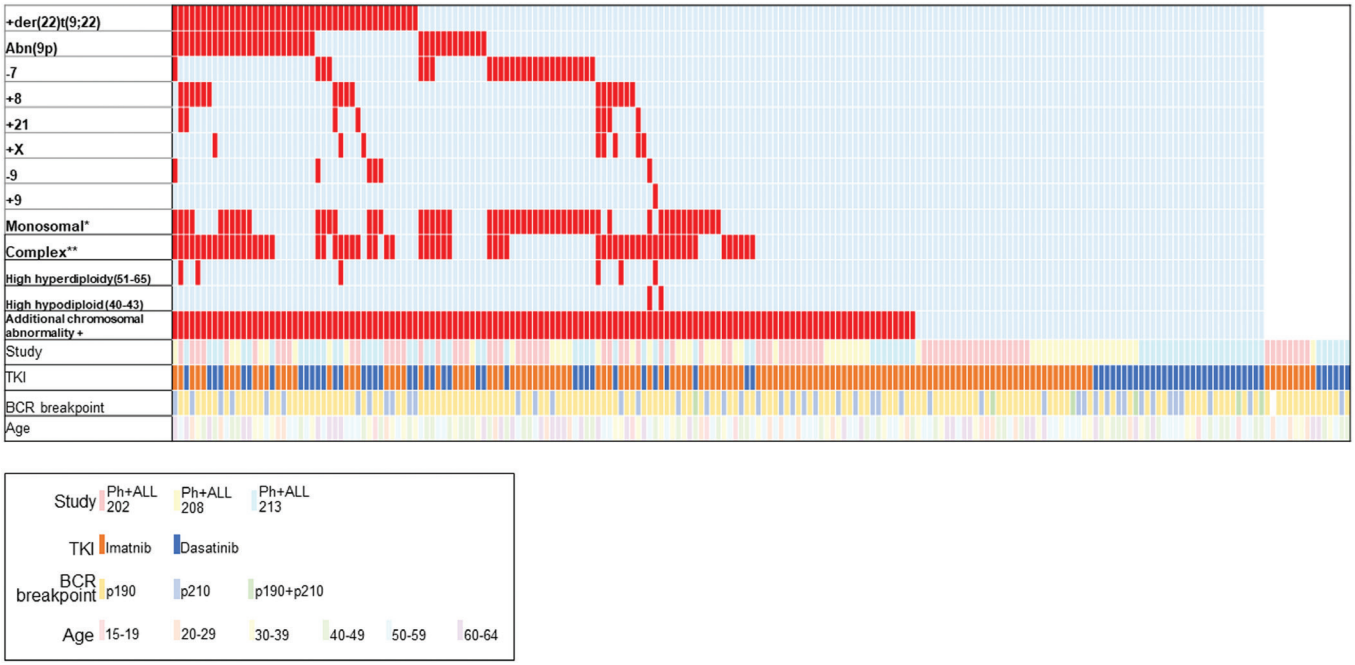


Figure 1. Landscape of additional chromosomal abnormalities. *Monosomal karyotype means 1 or more autosomal monosomy in addition to t(9;22) (–7 and –9 described above were also counted as monosomal). **Complex karyotype means 2 or more additional aberrations in addition to t(9;22) (ACAs described earlier were also counted as complex when there were at least 2 aberrations in addition to t[9;22]). ACA = additional chromosomal abnormalities.

CI, 61.7%-83.1%] versus imatinib: 50.6% [95% CI, 41.6%-59.0%] at 5 y; $P = 0.002$). OS with a landmark at 3 months was significantly different between patients who achieved molecular CR at 3 months and those who did not (molecular CR(+): 65.7% [95% CI, 56.6%-73.4%] versus molecular CR(–): 43.5% [95% CI, 24.8%-60.9%] at 5 y; $P = 0.02$).

At 5 years, leukemia-free survival (LFS) was 51.0% (95% CI, 43.6%-57.9%) in 198 patients who achieved CR1. LFS tended to be higher in patients treated with dasatinib compared with those treated with imatinib (dasatinib: 55.7% [95% CI, 42.6%-66.9%] versus imatinib: 47.6% [95% CI, 38.5%-56.2%] at 5 y; $P = 0.07$). LFS with a landmark at 3 months was significantly different between patients who achieved molecular CR at 3 months and those who did not (molecular CR(+): 55.5% [95% CI, 46.3%-63.8%] versus molecular CR(–): 32.6% [95% CI, 15.7%-50.8%] at 5 y; $P = 0.02$).

When divided into 4 groups of chromosomal abnormalities, (1) both +der(22)t(9;22) and a complex karyotype; (2) +der(22)t(9;22) alone; (3) a complex karyotype alone; and (4) others, OS and LFS were worse in patients with both +der(22)t(9;22) and complex karyotype (Suppl. Figure S2). In multivariate analysis, while coexistence of +der(22)t(9;22) and a complex karyotype was a significant risk factor for both OS and LFS, +der(22)t(9;22) alone or a complex karyotype alone were not significant risk factors (Figure 2A).

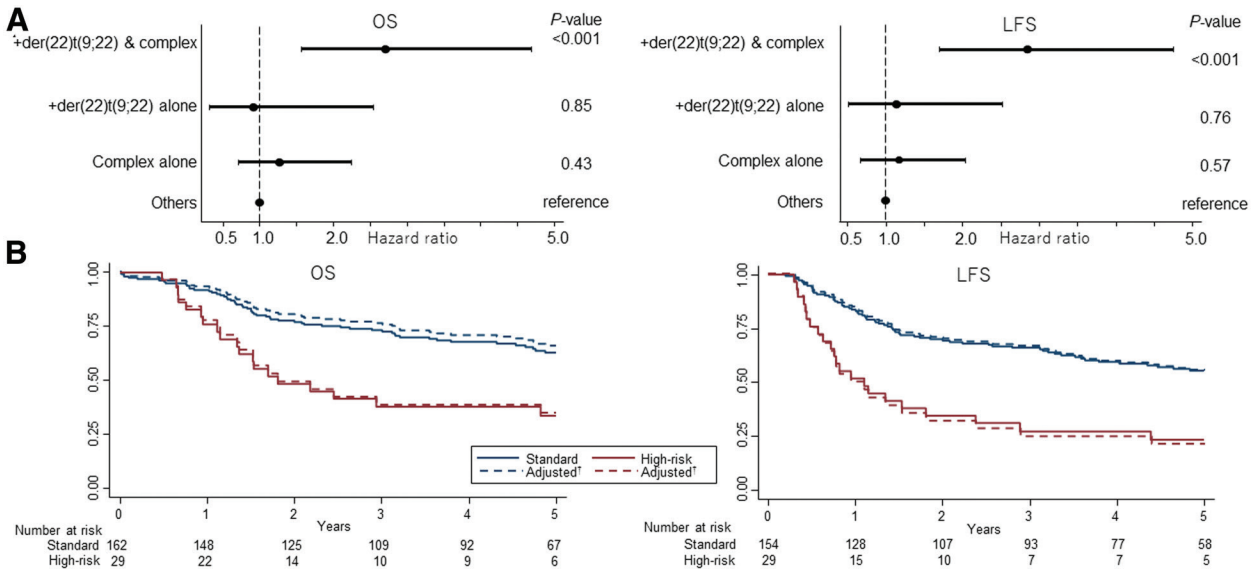
When the coexistence of +der(22)t(9;22) and a complex karyotype were considered high risk and the others are considered standard risk, both OS and LFS were significantly worse in high-risk patients compared with standard-risk patients (Figure 2B).

Patient characteristics by chromosomal risk are shown in Suppl. Table S2. There were no significant differences in baseline characteristics between the standard- and high-risk patients. The CR1 achievement rate was not significantly different between the standard- and high-risk patients (95.1% versus 100%; $P = 0.22$). In addition, the molecular CR rate at 3 months was not significantly different between the standard- and high-risk patients (79.8% versus 78.2%; $P = 0.86$). However, among patients who relapsed after achieving CR1, CR duration was significantly shorter in high-risk patients compared with standard-risk patients (0.68 versus 1.1 y; $P = 0.046$). The OS of high-risk patients was worse than that of low-risk patients, even when censored at the time of allo-SCT (1-y adjusted OS: 73.3% [95% CI, 54.6%-98.3%] versus 95.7% [95% CI, 92.0%-99.5%]).

Regarding the type of TKIs, although OS was significantly higher in standard-risk patients treated with dasatinib compared with standard-risk patients treated with imatinib (dasatinib: 85.2% [95% CI, 72.5%-92.3%] versus imatinib: 51.9% [95% CI, 41.7%-61.2%] at 5 y; $P < 0.001$), no significant differences in OS were observed between high-risk patients treated with dasatinib and high-risk patients treated with imatinib when post hoc analyses were performed (dasatinib: 33.7% [95% CI, 9.5%-60.4%] versus imatinib: 31.3% [95% CI, 11.4%-53.7%] at 5 y; $P = 0.55$). Similarly, although LFS tended to be higher in standard-risk patients treated with dasatinib compared with standard-risk patients treated with imatinib (dasatinib: 65.4% [95% CI, 49.8%-77.2%] versus imatinib: 49.3% [95% CI, 38.9%-58.9%] at 5 y; $P = 0.06$), no significant differences in LFS were observed between high-risk patients treated with dasatinib and high-risk patients treated with imatinib when post hoc analyses were performed (dasatinib: 19.2% [95% CI, 3.3%-45.0%] versus imatinib: 25.0% [95% CI, 7.8%-45.0%] at 5 y; $P = 0.54$).

Although it has been reported that +der(22)t(9;22) is an ACA with a poor prognosis[1], we clarified that prognoses differ depending on the coexistence of a complex karyotype. It is known that an ACA is often observed in Ph+ALL patients, but reports of whether ACAs affect prognosis are inconsistent: some studies have reported that ACAs were a poor prognostic factor[7,9] whereas others have reported that ACAs were not a poor prognostic factor.[10-12] Considering the types and combinations of ACAs, we were able to clarify a subgroup of ACAs with poor prognosis in Ph+ALL.

The cooccurrence of +der(22)t(9;22) and a complex karyotype was associated with a poor prognosis. In this high-risk combination of chromosomal abnormalities, not only hematological CR but also molecular CR could be achieved with the same probability



5-yearOS, LFS (%)

	Unadjusted OS	95%CI	Adjusted OS†	95%CI	Unadjusted LFS	95%CI	Adjusted LFS†	95%CI
Standard*	62.7	54.4-70.0	66.0	58.4-74.6	55.3	46.8-63.0	55.8	48.1-64.7
High-risk**	33.4	17.0-50.8	34.4	20.5-57.8	23.3	9.9-39.9	22.8	11.5-45.2

†Adjusted for age, WBC, and TKI.
* Karyotype other than high-risk karyotype. ** +der(22)t(9;22) & complex.

Figure 2. Risk of additional chromosomal abnormalities. (A) Forest plots for the adjusted hazard ratios and 95% confidence intervals in the multivariate analysis. (B). Survival according to the risk of ACAs. All covariates other than karyotype included in multivariate models were age, WBC, and TKI. ACA = additional chromosomal abnormalities; TKI = tyrosine kinase inhibitor; WBC = white blood cell.

as patients with standard risk, but the risk was characterized by early recurrence. In addition, improved survival with dasatinib instead of imatinib, which was observed in standard-risk patients, was not observed in high-risk patients. In this study, a complex karyotype was defined as the presence of at least 3 abnormalities, which meant that high-risk patients had 1 or more other abnormalities in addition to Ph of the main cell lineage and +der(22)t(9;22). It has been reported that ponatinib, a third-generation TKI, and/or blinatumomab, a bispecific T-cell engager, improves treatment results for Ph+ALL patients.[13,14] Because ponatinib is a multikinase inhibitor and blinatumomab is an immunotherapy drug, both of which act in addition to BCR-ABL1 kinase, they may be effective for Ph+ALL patients with high-risk chromosomal abnormalities. As ponatinib was approved in 2016 for relapsed/refractory Ph+ALL and blinatumomab was approved in 2018 for relapsed/refractory ALL in Japan, the effects of these new drugs will be clarified in future clinical trials.

Recently, the effect of genetic aberrations on prognosis has been reported by clinical studies of Ph+ALL. The presence of additional copy number alterations (CNAs) with the cooccurrence of IKZF1 plus CDKN2A/B and/or PAX5 has been associated with poor survival.[2,14] In another study, we are conducting genetic analysis using preserved specimens from clinical studies of Ph+ALL conducted at JALSG. Considering that several chromosomal abnormalities are reported to be associated with CNAs in ALL,[15] there may be genetic aberrations associated with the high-risk combination of ACAs identified in this study. The elucidation of associated genetic abnormalities may lead to new targeted therapies.

Data from 3 prospective studies conducted at JALSG in the TKI era were analyzed in this study. Although some treatment improvements have been made between the studies, the principals of the chemotherapy regimens remained the same. Therefore, pooling data from the 3 studies was considered suitable for identifying leukemias with high-risk biological characteristics using a large number of cases that are difficult to accumulate in a single clinical study. As a result, we were able to identify a high-risk ACA combination that was less frequent (14%) by analyzing >200 de novo Ph+ALL patients.

In conclusion, the coexistence of +der(22)t(9;22) and a complex karyotype was identified as a high-risk combination of ACAs in Ph+ALL. Multiple ACAs are often observed in Ph+ALL, leading to identifying this subgroup with a poor prognosis. It was characterized by early relapse, although remission could be achieved at the same rate as standard-risk Ph+ALL. Further molecular genetic elucidation and the establishment of effective therapeutic strategies are warranted.

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AUTHOR CONTRIBUTIONS

SN, IS, SF, YH, and YA designed the research, performed the statistical analysis, interpreted the data, and wrote the article. N Doki, S Kurahashi, YU, N Dobashi, TM, YT, and MT provided the data of patients. YA, S Kako, TI, and TF collected the data of patients regarding TRUMP database. SO, YI, HK, IM, YM collected the data of patients regarding JALSG studies. All authors reviewed and approved the final draft.

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