Original Article

The Effect of Hematopoietic Stem Cell Transplantation on Treatment Outcome in Children with Acute Lymphoblastic Leukemia

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Running Title: Effect of HSCT on Outcome in Pediatric ALL

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Abstract

Purpose
Hematopoietic stem cell transplantation (HSCT) has been an important method of treatment in the advance of pediatric acute lymphoblastic leukemia (ALL). The indications for HSCT are evolving and require updated establishment. In this study, we aimed to investigate the efficacy of HSCT on the treatment outcome of pediatric ALL, considering the indications for HSCT and subgroups.

Materials and Methods
A retrospective analysis was conducted on ALL patients diagnosed and treated at a single center. Risk groups were categorized based on age at diagnosis, initial white blood cell count, disease lineage (B/T), and cytogenetic study results. Data on the patients’ disease status at HSCT and indications of HSCT were collected. Indications for HSCT were categorized as upfront HSCT at 1st complete remission, relapse, and refractory disease.

Results
Among the 549 screened patients, a total of 418 patients were included in the study; B-ALL (n=379) and T-ALL (n=39). HSCT was conducted on a total of 106 patients (25.4%), with a higher frequency as upfront HSCT in higher risk groups and specific cytogenetics. The overall survival (OS) was significantly better when done upfront than in relapsed or refractory state in T-ALL patients (p=0.0016). The KMT2A-rearranged ALL patients showed superior event-free survival (p=0.0023) and OS (p=0.0221) when HSCT was done as upfront treatment.

Conclusion
HSCT had a substantial positive effect in a specific subset of pediatric ALL. In particular, frontline HSCT for T-ALL and KMT2A-rearranged ALL offered a better prognosis than when HSCT was conducted in a relapsed or refractory setting.
Keywords

Precursor cell lymphoblastic leukemia-lymphoma, Hematopoietic stem cell transplantation, Survival, $KMT2A$, precursor T-cell lymphoblastic leukemia-lymphoma
Introduction

The cure rate for acute lymphoblastic leukemia (ALL) in children ranges 80-90% due to the progress made in chemotherapy and conservative treatment [1]. Additionally, the advancement of hematopoietic stem cell transplantation (HSCT) has significantly contributed to improving the outcomes of ALL treatment by combining intensive preparative radiation and/or chemotherapy with the graft-versus-leukemia (GvL) effect [2].

HSCT has been recommended for patients diagnosed with ALL who are in their first complete remission (CR1) but are classified as being in the very high-risk group, indicating that they are expected to have unsatisfactory results with conventional chemotherapy. Historically, Philadelphia chromosome-positive (Ph+) ALL, hypodiploidy, KMT2A rearrangement, and induction failure have been classified as very high-risk diseases which are considered to benefit from HSCT at CR1 [3].

Nevertheless, the introduction of tyrosine kinase inhibitors (TKI) and more recent chimeric antigen receptor (CAR)-T cell therapy is anticipated to decrease the need for HSCT. On the other hand, advancements of HSCT technology have led to a reduction in toxicity, increase in HSCT with an alternative donor, and significant improvement in HSCT outcomes [4]. At present, there are various perspectives regarding the appropriate criteria for administering HSCT, both in practical use and clinical studies.

In this study, our objective was to examine the treatment outcomes based on the indications for HSCT in patients with ALL treated at our institution over the past 25 years. We intended to assess the effectiveness of employing HSCT based on different subgroups of pediatric ALL.
Materials and Methods

1. Patient and Treatment

We retrospectively reviewed the medical records of patients diagnosed with ALL and treated at the Department of Pediatrics at Samsung Medical Center between 1994 and 2019. This study received approval from the Institutional Review Board of Samsung Medical Center (approval No. 2022-03-122-002), and the need for consent was waived by the board.

Patients were categorized into risk groups based on age at diagnosis, initial white blood cell (WBC) count, disease lineage (B/T), and cytogenetic study results. Those who had any of the conditions listed below were classified as being at very high-risk: Philadelphia chromosome, t(4;11) of an infant, and hypodiploidy (defined as chromosome <45 by cytogenetics) of B-cell ALL patients, hyperleukocytosis (defined as initial WBC of 200,000/uL or above) in T-cell ALL patients, and induction failure of any immunophenotype. Patients older than 1 year old and younger than 10 years old at diagnosis without CNS disease or testis involvement, also without unfavorable cytogenetics were defined as standard risk. But if the patient had taken steroids before diagnosis, they were placed in the high-risk group. All the patients excluded from the standard or very high-risk group were also defined as high risk.

Patients with Down syndrome or acute leukemia with ambiguous lineage were not included in the risk group analysis. For treatment outcome analysis, cytogenetic groups were categorized into specific groups, including the Philadelphia chromosome, KMT2A rearrangement (defined as t(v;11q23.3) with any fusion partner), hypodiploidy, hyperdiploidy, ETV6::RUNX1, and others (other cytogenetic findings excluding front objects).

Standard-risk group patients were treated with a 3-drug (vincristine, prednisolone, L-asparaginase) induction, while other patients received a 4-drug (vincristine, prednisolone, L-
asparaginase, daunorubicin) induction. Treatment continued according to the initially classified risk group for patients in complete remission after induction chemotherapy. Those with residual disease or those needing to be classified as high-risk based on cytogenetic tests received intensified chemotherapy. HSCT was indicated for very high-risk and relapsed ALL patients.

2. Data Collection and Definition

Data on the patients’ disease status at the time of HSCT and indications of HSCT were collected. The indication of HSCT was classified into three types: Upfront treatment for individuals in very high-risk group, relapsed disease, and refractory disease. The cause of death was categorized as leukemia progression or non-relapse mortality (NRM). NRM encompassed all deaths not attributable to relapse of underlying disease, including second malignant neoplasm (SMN).

3. Statistical Analysis

Descriptive analyses were conducted for age, sex, risk group, and cytogenetic groups. Age, sex, risk group, cytogenetic group, and central nervous system (CNS) status at diagnosis were compared between the groups with and without HSCT using the chi-square test or Fisher's exact test. Survival analysis was performed using the Kaplan-Meier analysis with differences compared by the log-rank test. The Cox proportional-hazards model was used for multivariable analyses of prognostic factors.

All statistical analyses were performed using STATA/MP 17.0 (StataCorp LLC, Texas). The significance level for statistical tests, which used two-sided probability, was set at p<0.05.
Results

1. Patients and Treatment

A total of 549 patients diagnosed with or treated for ALL underwent screening. Out of these, 89 individuals were excluded from the study. Among them, 73 were transferred from another hospital, 14 were transferred to another hospital before or during treatment, and two patients died before receiving therapy. The special population with acute leukemia of ambiguous lineage (n=39) and acute leukemia with Down syndrome patients (n=3) were excluded also. A total of 418 patients, including 379 B-ALL patients and 39 T-ALL patients, comprised the study (Fig. 1). The median age at diagnosis was 5.3 years old (range, 0.0-26.5), and 54.5% of patients were male (n=228). The median follow-up time was 97.4 months (range, 0.7-25.2) in the total patients and 109.4 months (range, 5.0-252.4) in alive patients.

Among the total patients, 106 (25.4%) underwent HSCT, which was performed more frequently in T-ALL patients. (B-ALL, n=86 of 379, 22.4%; T-ALL, n=20 of 39, 51.3%; \(P<0.001\)) When the patients were divided based on their HSCT status, there was no difference in age, sex, or CNS status between the groups. However, the rate of HSCT was significantly different by risk group and cytogenetic group (Table 1).

The indications for HSCT varied significantly based on the cytogenetic group (Table 2). Regarding the Philadelphia chromosome, hypodiploidy, and \(KMT2A\) rearrangement, HSCT was typically scheduled upfront at CR1. However, for cases of hyperdiploidy or \(ETV6::RUNXI\), HSCT was performed when the disease relapsed or became refractory to treatment (Table 2). No significant variation in the indication of HSCT was observed based on the period of HSCT. (\(p=0.156\)) Secondary malignancy was developed in a total of five (1.2%) patients.
2. Survival Outcome

The 5-year overall survival (OS) of the total patients was 84.9% (95% CI, 84.6-91.2). The 5-year OS in the patients treated without HSCT was 95.4% (95% CI, 91.9-96.8), and in those who were treated with HSCT was 56.0% (95% CI, 45.1-65.6), respectively (p<0.0001). The 5-year OS of the patients who underwent upfront HSCT was 70.3%, those who underwent HSCT for refractory ALL was 57.3%, and those who underwent HSCT for relapsed disease was 58.6%. (p=0.1707) The period of HSCT (p=0.1464) was not a significant factor related to the OS.

The 5-year OS for B-ALL were 95.5% (95% CI, 91.9-97.5) in patients who did not undergo HSCT and 58.3% (95% CI, 46.2-68.5) in patients who underwent HSCT (p<0.0001). The 5-year OS for T-ALL was 93.9% (95% CI, 64.2-99.1) in non-HSCT and 45.5% (95% CI, 19.7-68.2) in HSCT group, respectively (p=0.0036). Although the OS was significantly different between patients in each risk group (p<0.0001), there was no significant difference of OS between risk groups in the patients who underwent HSCT (5yr-OS 61.5% (standard-risk, 95% CI 42.8-86.1) vs. 33.9% (high-risk, 95% CI 14.1-55.0) vs. 62.3% (very high-risk, 95% CT 48.3-73.5), p=0.1013). The OS was not significantly different according to indication of HSCT in total patients (p=0.1707) and B-ALL patients (p=0.2954), but was significantly better when HSCT was performed upfront compared to those in relapsed or refractory state in T-ALL patients (p=0.0016) (Fig. 2).

When analyzing the patients who underwent upfront HSCT (N=79), the type of donor (matched, n=58; haploidentical, n=14; cord blood, n=4, not available, n=3) showed no significant relation to event-free survival (EFS) (p=0.8478) and OS (p=0.5283). The adoption
of total body irradiation (TBI) also did not affect EFS ($p=0.1574$) and OS ($p=0.5469$).

In our study, there were 22 patients with $KMT2A$ rearrangement, including 13 infants. Among $KMT2A$-rearranged patients, 11 patients had t(4;11) translocation and other 11 patients had t(v;11q23.3) ($KMT2A$-r) with a different counterpart. Patients with t(4;11) and patients with other $KMT2A$ rearrangement demonstrated a 5-year OS of 63.6%, both. ($p=0.9002$) Cumulative incidence of NRM in $KMT2A$-rearranged patients lower than 1 yrs old and over 1 yr old was 23% and 0%, respectively.

Since 2007, imatinib has been administered to patients with newly diagnosed Ph+ ALL as part of their treatment. The OS rate for patients with Ph+ ALL who received treatment prior to 2007 was 50%, with 4 out of 8 patients surviving. Conversely, the OS for Ph+ ALL patients treated after 2007 was 66.7%, with 8 out of 12 patients surviving. ($p=0.5005$)

3. Impact of HSCT on Treatment Outcome

We investigated whether HSCT as the primary treatment option affected subsequent relapse or survival in special groups. Since upfront HSCT was performed in every patient with Ph+ ALL, it was not feasible to examine the impact of HSCT in this particular group. In addition, none of the patients with hyperdiploidy underwent HSCT as their upfront treatment, and there were only three patients with hypodiploidy in the total cohort, thus excluded from the analysis.

For patients in the $KMT2A$ rearrangement and other cytogenetics group, we analyzed the effect of upfront HSCT on EFS. The $KMT2A$-rearranged ALL patients showed superior EFS ($p=0.0023$) and OS ($p=0.0221$) when HSCT was done upfront, compared to the patients who underwent HSCT in CR2 or more. The patients in the other cytogenetics group showed
superior EFS ($p=0.0001$) and OS ($p=0.001$) in the patients without upfront HSCT (Fig. 3).

A total of 16 patients experienced induction failure after the initial treatment. Out of the sixteen patients who did not achieve remission after induction, twelve had B-ALL and four had T-ALL. Except for one patient per each immunophenotype, HSCT was done at CR2 for other fourteen patients. Among the patients who did not adopt HSCT at CR1, one T-ALL patient survived, but one B-ALL with $KMT2A$ rearrangement expired due to disease progression. The 5-year OS rate of the patients with induction failure was 81.25% (95% CI, 52.46-93.54).

4. Treatment after Relapse

A total of 61 patients relapsed, with 23 of them surviving (5-yr OS 50.0%, 95% CI 37.0-67.1). Among these, 12 patients who had not received HSCT before were salvaged with HSCT after relapse. Other 8 survivors were not subjected to HSCT and were salvaged with chemotherapy, either alone or in combination with radiotherapy. The reason for not receiving HSCT at CR2 in these patients was late relapse or isolated CNS relapse. In addition, there were 3 patients who relapsed after HSCT but were successfully treated with chemotherapy without repetitive HSCT after relapse (Table 3). All these patients presented prominent graft-versus-host disease (GvHD) following relapse.

Discussion

Allogeneic HSCT is anticipated to exert a consolidative radio-chemotherapeutic effect as well as a GvL effect, thus preventing relapse in individuals with ALL who are difficult to cure with chemotherapy alone. Nevertheless, there is no distinct consensus on which patients...
need HSCT, and frequent modifications are required due to advancements in treatment, represented by TKI in Ph+ ALL, immunotherapy, and cellular therapy [5]. Improved minimal residual disease (MRD) diagnostics are another factor changing the decision-making process in ALL treatment, including HSCT [6].

Historically, Ph+ ALL, hypodiploidy, KMT2A rearrangement, and induction failure have been classified as very high-risk diseases considered to benefit from HSCT at CR1. However, recent pediatric ALL studies present varied opinions.

ALL with KMT2A rearrangement is anticipated to show a poor outcome with a high rate of relapse. Historically, HSCT was recommended for infants with KMT2A-rearranged ALL. However, recent Children’s Oncology Group (COG) studies did not adopt HSCT based on their previous data, indicating that the 5-year EFS did not differ between the patients with or without HSCT, both being less than 50% [7,8]. Comparably, Interfant-99 study which incorporated HSCT after intensive chemotherapy in high-risk KMT2A-rearranged infant ALL patients, resulted in 60.9% of disease-free survival (DFS). In the subgroup with age less than six months and either a poor response to steroids on day 8 or leukocytes greater than or equal to 300 g/L, the DFS was significantly greater when HSCT was conducted compared to when it was not [9,10]. In contrast, a recent retrospective study of non-infant childhood ALL with KMT2A rearrangements revealed that EFS did not improve even after HSCT [11].

At our center, HSCT has been recommended for all infants with KMT2A rearrangement. However, if the child was diagnosed beyond the age of 1 year, KMT2A rearrangement was not considered a sole reason for HSCT during CR1. Even though the modest size of our study population, upfront HSCT in CR1 resulted in superior RFS and EFS for patients of all ages with KMT2A rearrangement. Nevertheless, the NRM was high in KMT2A-rearranged infant
ALL, indicating it is crucial to effectively manage treatment-related toxicity in this group.

It is evident from our findings that the cure rate for KMT2A-rearranged ALL patients is unsatisfactory when treated just with chemotherapy. Recent investigations have been carried out on targeted therapy (e.g. menin inhibitor) and cell therapy as potential alternatives [12]. Nevertheless, research on these treatments is not prioritized, thus HSCT continues to serve a function.

Although the number of T-ALL patients in each group were small, the OS was considerably better when HSCT was done upfront (n=17) than when HSCT was done for relapsed or refractory disease (n=3). A recent study on T-ALL in adults reported a survival benefit when HSCT was performed upfront [13]. Meanwhile, another study conducted on adolescent and adult T-ALL patients showed superior survival rate in patients who underwent upfront HSCT not only at CR status but also at PR status [14]. The effect of HSCT in T-ALL can be suggested by the fact that GvHD reduced the likelihood of relapse in T-ALL patients [15]. Nevertheless, recent research has demonstrated that the relapse rate is decreased when nelarabine is administered upfront in T-ALL [16]. The necessity for HSCT is expected to decrease further if nelarabine or new drugs could be implemented in indicated patients.

In our study group, all Ph+ ALL patients underwent HSCT upfront in CR1, so it was impossible to know the impact of HSCT in this group. The 5-yr OS and EFS rates of Ph+ ALL patients in this study were 59.8% (95% CI, 35.5-75.5%) and 50.5% (95% CI, 27.1-69.2%). The 5-yr OS for patients with Ph+ ALL who received imatinib or did not get imatinib was 66.7% and 50%, respectively, which was comparable to recent prospective studies [17,18].

With the incorporation of TKI into treatment, the requirement for HSCT has considerably decreased in patients with Ph+ ALL. A recent joint study of COG and European
intergroup study reported that when dasatinib was combined with chemotherapy, a similar survival outcome was achieved even with limited use (14%) of HSCT [19]. Additionally, promising data are emerging for the use of frontline blinatumomab in combination with TKIs for newly diagnosed adult patients with Ph+ ALL [20-22]. Therefore, the implementation of targeted therapy and immunotherapy in Ph+ ALL is expected to improve treatment outcomes, leading to a reduction in the need for HSCT. Now in our center, Ph+ ALL patients with good initial response are not considered for upfront HSCT, but are treated with chemotherapy and TKI.

In our study, although a small subset, there were patients who relapsed post-HSCT but could achieve a long-term control of leukemia without a 2nd HSCT, possibly from the GvL effect. These cases demonstrate the importance of HSCT as a form of immunotherapy in the control of ALL. A comprehensive registry study of CIBMTR showed that ALL patients who experience acute or chronic GvHD after HSCT had a reduced likelihood of relapse [2]. Additionally, a recent study on Ph+ ALL demonstrated a lower relapse rate in HLA-mismatched unrelated bone marrow transplantation (uBMT) compared to HLA-matched uBMT, implying the possible GvL effect [23].

This study has several limitations. First, although the measurement of MRD response holds significance as a prognostic factor and plays a crucial role in determining the eligibility of HSCT, the early-period patients did not undergo MRD assessment, limiting the analysis of relevant data to this factor. Second, statistical significance analysis was challenging in several subgroups due to the limited sample size in each category. In the Ph+ ALL group, which received uniform HSCT at CR1, and the hypodiploidy group, for which there were insufficient numbers, the clinical significance of HSCT could not be determined. Previous studies proposed that TBI and GvHD could improve post-HSCT outcomes in ALL. [2, 24] However, our study...
was unable to validate these findings, potentially due to the limited sample size. Third, new categories with documented clinical significance, such as Ph-like ALL or TCF3::HLF rearranged ALL, could not be diagnosed during the time period covered by this study, so these data could not be included.

Nevertheless, despite the increasing use of targeted therapy and immunotherapy, this study is noteworthy for identifying a specific population that is challenging to treat effectively with chemotherapy alone. This is expected to provide information on who will be prioritized indications of further clinical trials. Moreover, as this study was carried out on patients treated at a single institution, it holds significance due to the ability to implement a uniform treatment approach. This also allowed for a clear identification of the indication for HSCT in each individual.

Currently, the application of CAR-T cell therapy is being expanded in pediatric ALL. The implementation of this novel therapy is given higher priority in populations that continue to experience unfavorable results. Nevertheless, due to the observed relapse rate of up to 50% after CAR-T cell therapy, ongoing attempts are being undertaken to mitigate recurrence by using HSCT following CAR-T cell therapy [25]. Further investigation is necessary to examine the outcomes when these two treatments are used in combination. Moreover, it is imperative to carry out comparative studies to determine whether cell therapy or targeted therapy can function as feasible substitutes for HSCT in groups that can benefit from HSCT, as insufficient research exists that directly compares and analyzes the outcomes of HSCT with novel therapies based on specific indications.

In conclusion, our study examined the efficacy of HSCT for individual risk groups in treating ALL, and it revealed that HSCT had a considerable positive impact in certain instances.
For *KMT2A*-rearranged ALL and T-ALL, the survival outcome was superior when upfront HSCT was performed, as opposed to when treatment was planned using chemotherapy alone. The immunological mechanism of HSCT for ALL was verified by observing cases where relapse was well managed through the GvL effect, even in instances of relapse following HSCT. For patients with a low probability of being cured by chemotherapy alone, it is advisable to consider HSCT as an adjunctive therapy. Nevertheless, it is crucial to always consider the potential toxicity associated with HSCT. Particular attention is necessary when dealing with cases of infants or second HSCT following relapse. In these populations, HSCT with caution will be necessary to minimize toxicity as much as possible.

**Ethical Statement**

This study received approval from the Institutional Review Board of Samsung Medical Center (approval No. 2022-03-122-002), and the need for consent was waived by the board.

**Author Contributions**

Conceived and designed the analysis: Ju HY, Yoo KH.

Collected the data: Ju HY, Lee NH, Yi ES, Choi YB, Koo HH, Yoo KH.

Contributed data or analysis tools: Ju HY, Lee NH, Kim SJ, Hyun JK, Cho HW, Lee JK, Sung KW, Koo HH, Yoo KH.

Performed the analysis: Ju HY.

Wrote the paper: Ju HY.

Reviewed and edited the paper: Ju HY, Lee NH, Yi ES, Choi YB, Kim SJ, Hyun JK, Cho HW, Lee JK, Sung KW, Koo HH, Yoo KH.
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Conflict of Interest

Conflict of interest relevant to this article was not reported.

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References


Fig 1. Study population.

*ALAL: Acute leukemia of ambiguous lineage
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total patients (n=418) (%)</th>
<th>HSCT group(^a) (n=106) (%)</th>
<th>No HSCT group (n=312) (%)</th>
<th>p</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>B-ALL</td>
<td>379 (90.7)</td>
<td>86 (81.1)</td>
<td>293 (93.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>T-ALL</td>
<td>39 (9.3)</td>
<td>20 (18.9)</td>
<td>19 (6.1)</td>
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<tr>
<td>Median age at diagnosis (range)</td>
<td>5.2 (0.0-26.5)</td>
<td>6.4 (0.0-19.8)</td>
<td>5.2 (0.3-26.5)</td>
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<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
<td>228 (54.5)</td>
<td>66 (62.3)</td>
<td>162 (51.9)</td>
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<td>Female</td>
<td>190 (45.5)</td>
<td>40 (37.7)</td>
<td>150 (48.1)</td>
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<tr>
<td>Risk group</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard risk</td>
<td>206 (49.3)</td>
<td>18 (17.0)</td>
<td>188 (60.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>High risk</td>
<td>141 (33.7)</td>
<td>22 (20.8)</td>
<td>119 (38.1)</td>
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<tr>
<td>Very high risk</td>
<td>71 (17.0)</td>
<td>66 (62.3)</td>
<td>5 (1.6)</td>
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<tr>
<td>Cytogenetic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR::ABL1 translocation</td>
<td>20 (4.8)</td>
<td>20 (18.9)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
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<tr>
<td>KMT2a rearrangement</td>
<td>22 (5.3)</td>
<td>17 (16.0)</td>
<td>5 (1.6)</td>
<td></td>
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<tr>
<td>Hyperdiploidy</td>
<td>93 (22.3)</td>
<td>8 (7.6)</td>
<td>85 (27.2)</td>
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<tr>
<td>Hypodiploidy</td>
<td>3 (0.7)</td>
<td>2 (1.9)</td>
<td>1 (0.3)</td>
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<tr>
<td>ETV6::RUNX1</td>
<td>69 (16.5)</td>
<td>3 (2.8)</td>
<td>66 (21.2)</td>
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<tr>
<td>Others</td>
<td>211 (50.5)</td>
<td>56 (52.8)</td>
<td>155 (49.7)</td>
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<tr>
<td>CNS status at diagnosis</td>
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<td>CNS 1</td>
<td>382 (91.4)</td>
<td>94 (88.7)</td>
<td>287 (92.0)</td>
<td>0.773</td>
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<td>CNS 2</td>
<td>26 (6.2)</td>
<td>9 (8.5)</td>
<td>16 (5.1)</td>
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<tr>
<td>CNS 3</td>
<td>10 (2.4)</td>
<td>3 (2.8)</td>
<td>7 (2.2)</td>
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<tr>
<td>N/A</td>
<td>2 (0.5)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
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<td>Period of HSCT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2000-2009</td>
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<td>45 (42.1)</td>
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<tr>
<td>2010-2015</td>
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<td>32 (29.9)</td>
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<tr>
<td>2016-2021</td>
<td></td>
<td>30 (28.0)</td>
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</table>

\(^{a}\)Two patient who underwent HSCT for other indication (secondary AML) was excluded from the analysis.
Table 2. Indication of HSCT and Cause of Death According to Cytogenetic Groups

<table>
<thead>
<tr>
<th>Cytogenetic group</th>
<th>Indication of HSCT</th>
<th>Cause of Death</th>
<th>p</th>
<th>Disease progression</th>
<th>Nonrelapse death</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planned at 1st CR</td>
<td>Refractory (n=10)</td>
<td>Relapse (n=28)</td>
<td>p</td>
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</tr>
<tr>
<td>Philadelphia chromosome</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>KMT2A rearrangement</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypodiploidy</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ETV6::RUNX1a)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>33</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>19b)</td>
<td></td>
</tr>
</tbody>
</table>

a) There was one patient with ETV6::RUNX1 who lost follow up and died 2 years later. As the cause of death is unknown, the patient was removed from analysis of the cause of death. b) Includes one death from second malignant neoplasm.
Table 3. Characteristics of patients who relapsed after HSCT, and were treated without second HSCT

<table>
<thead>
<tr>
<th>Case</th>
<th>Immunophenotype</th>
<th>Cytogenetics(^a)</th>
<th>HSCT at 1(^{st}) CR</th>
<th>Relapse Site</th>
<th>Relapse Interval(^b)</th>
<th>Treatment after relapse</th>
<th>GvHD</th>
<th>Last status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B-ALL</td>
<td>Philadelphia chromosome</td>
<td>Yes (related PBSCT)</td>
<td>1(^{st}), BM</td>
<td>15mo</td>
<td>Unrelated PBSCT</td>
<td>Acute (1)</td>
<td>8yr 10mo disease-free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2(^{nd}), breast</td>
<td>24mo</td>
<td>CTx, Mass excision</td>
<td>Chronic (moderate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3(^{rd}), CNS</td>
<td>38mo</td>
<td>RTx, TKI, IT CTx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>B-ALL</td>
<td>Hyperdiploidy</td>
<td>No</td>
<td>1(^{st}), BM</td>
<td>25mo</td>
<td>Unrelated PBSCT</td>
<td>Acute (4)</td>
<td>3yr 11mo disease-free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2(^{nd}), bone</td>
<td>44mo</td>
<td>CTx (blinatumomab, clofarabine)</td>
<td>Chronic (moderate)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>T-ALL (ETP-ALL)</td>
<td>(STIL::TAL1) rearrangement</td>
<td>Yes (related PBSCT)</td>
<td>BM</td>
<td>8mo</td>
<td>CTx (nelarabine)</td>
<td>Acute (2)</td>
<td>3yr disease-free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chronic (severe)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Cytogenetic abnormality at initial diagnosis; \(^b\)Time between initial diagnosis and relapse.
**Fig. 2.** Survival outcome according to clinical factors and treatment. (A) Overall survival of total patients with or without HSCT, (B) Overall survival of the patients who underwent HSCT (by indication), (C) Overall survival of total patients according to HSCT period, (D) Overall survival of B-ALL patients with or without HSCT, (E) Overall survival of T-ALL patients with or without HSCT, (F) Overall survival of patients of B-ALL patients who underwent HSCT, by indication, (G) Overall survival of patients of T-ALL patients who underwent HSCT, by indication, (H) Overall survival by cytogenetic groups, with or without HSCT.
Fig. 3. Effect of HSCT on treatment result in different subgroups, based on whether HSCT is adopted as primary treatment or not. (Other cytogenetics group: other than KMT2A, Ph+, hypodiploidy, hyperdiploidy, ETV6::RUNX1). (A) Event-free survival of KMT2A-rearranged ALL, (B) Overall survival of KMT2A-rearranged ALL, (C) Event-free survival of Other cytogenetics group, (D) Overall survival of Other cytogenetics group.