Original Article

Delayed Diagnostic Interval and Survival Outcomes in Pediatric Leukemia: A Single-Center, Retrospective Study

Kosuke Tamefusa[1,2], Motoharu Ochi[2], Hisashi Ishida[2], Takahiro Shiwaku[2], Kiichiro Kanamitsu[2,3], Kaori Fujiwara[2], Yasuhisa Tatebe[4], Naomi Matsumoto[5], Kana Washio[2], Hirokazu Tsukahara[1,2]

[1]Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[2]Department of Pediatrics, Okayama University Hospital, Okayama, Japan

[3]Department of Pediatrics, Okayama Medical Center Hospital, Okayama, Japan

[4]Department of Pharmacy, Okayama University Hospital, Okayama, Japan

[5]Department of Epidemiology, Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

***Corresponding author:**

Kosuke Tamefusa, MD, Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

E-mail: pblq6jkh@s.okayama-u.ac.jp

Tel: +81-86-235-7249; fax: +81-86-221-4745

Running title: Diagnostic interval in pediatric leukemia

Abstract word count: 187

Manuscript word count: 3009

Number of references: 23

Number of figures: 2

Number of tables: 2

Number of supplemental figures: 5

Number of supplemental tables: 4

Abbreviations	
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
CI	confidence interval
DI	diagnostic interval
EFS	event-free survival
IQR	interquartile range
NCI-SR	standard risk according to National Cancer Institute criteria
OS	overall survival
T-ALL/T-LL	T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma

1. What is the new aspect of your work?

In this study, we focused on the diagnostic interval (DI), defined as the duration of time from the onset of leukemic symptoms to diagnosis, and assessed whether a prolonged DI is associated with survival of patients with pediatric leukemia.

2. What is the central finding of your work?

The median DI was 20 days, and a prolonged DI (≥30 days) showed no association with the survival of children with leukemia.

3. What is (or could be) the specific clinical relevance of your work?

If a precise classification of leukemia biology is available for pediatric patients, a prolonged DI may have little impact on the prognosis of these patients.

Abstract

Objective:

This study primarily focused on the diagnostic interval (DI), defined as the duration from the onset of leukemic symptoms to diagnosis. We investigated whether a prolonged DI is associated with the outcomes of pediatric leukemia.

Methods:

We retrospectively collected data of children with newly diagnosed pediatric leukemia at Okayama University Hospital from January 2007 to December 2022. Survival analyses were conducted using Kaplan–Meier methods, and an unadjusted analysis to compare differences in survival was performed using the log-rank test.

Results:

In total, 103 children with leukemia were included in the analysis. The median DI was 20 days (interquartile range, 9.5–33.5 days). A prolonged DI (≥30 days) demonstrated no association with either 5-year event-free survival (70.1% for <30 days and 68.3% for ≥30 days, $P = 0.99$, log-rank test) or overall survival (84.7% for <30 days and 89.4% for ≥30 days, $P = 0.85$, log-rank test).

Conclusions:

A prolonged DI was not associated with the survival of children with leukemia. If a precise classification of leukemia biology is provided for pediatric patients, a prolonged DI may have little impact on the prognosis of these patients.

Key words: Diagnostic interval, Leukemia, Pediatric, Survival

Introduction

The diagnostic interval (DI) in pediatric cancer is a matter of concern for physicians, and several studies focusing on the DI have been reported.[1–5] Knowledge of whether a prolonged DI has a positive or negative impact on the outcome of pediatric cancer is of clinical significance. If the association between a prolonged DI and the survival outcome has a non-negative impact, we would be able to provide valuable information to patients' guardians. A prolonged DI can markedly heighten anxiety for both children and their parents, potentially leading to a negative impact on their subsequent experience with cancer care.

Childhood leukemia is the most common pediatric cancer and the leading cause of disease-related death among children in developed countries.[6–9] Although the survival of childhood leukemia has improved during the past few decades, relapse and refractory disease remain significant challenges.[6–8] A systematic review showed that the median time to diagnosis of acute leukemia from the onset of symptoms was <3 weeks; this was shorter than the median time to diagnosis of other pediatric solid cancers, reflecting the rapid progression of leukemia.[5] However, a prolonged time to diagnosis of leukemia is unavoidable in some patients because of the rarity of pediatric leukemia and the nonspecific initial symptoms of the disease.[10] In the abovementioned systematic review, the DI of pediatric leukemia was shorter for lymphoid leukemia than for myeloid leukemia.[5] Although the difference in the DI

is considered to be affected by leukemic biology, the difference in the DI according to leukemic subtypes has not been well studied.

Whether a prolonged DI adversely affects the survival of patients with pediatric leukemia is controversial. In Canadian studies, the time to diagnosis was not associated with the outcome of children with acute lymphoblastic leukemia (ALL).[3,11] By contrast, a Chinese study showed that a longer time to diagnosis negatively affected the outcome of pediatric ALL.[4] Furthermore, the definitions of the DI differed among these studies.

The present study was performed to describe the DI based on various clinical factors and evaluate its association with the survival of children with leukemia.

Methods

Study design and population

We retrospectively collected data from the electronic medical records of patients diagnosed with pediatric leukemia at Okayama University Hospital, which is a tertiary care university hospital, from January 2007 to December 2022. The catchment area served by Okayama University Hospital mainly includes Okayama, Hiroshima, Hyogo, Kagawa, Ehime, Tottori, Kochi, Yamaguchi, and Shimane prefectures. The inclusion criterion was newly diagnosed leukemia in patients aged 0 to 18 years. Patients who initiated chemotherapy for leukemia before their diagnosis, patients who were transferred to our hospital after initiating

chemotherapy for leukemia, and patients with myeloid proliferations related to Down syndrome were excluded. Patients with B-cell precursor ALL (BCP-ALL) were categorized as standard risk according to the National Cancer Institute criteria (NCI-SR) if they had neither an initial leukocyte count of >50 × 10^9/L nor an age of >10 years.[6] We also defined patients with *ETV6::RUNX1* or hyperdiploidy as having low-risk ALL. Most of the children with BCP-ALL were treated according to either the Japan Association of Childhood Leukemia Study (JACLS) ALL-02 protocol or the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) ALL-B12 protocol. The predominant treatment protocol for children with T-cell ALL and lymphoblastic lymphoma (T-ALL/T-LL) was either the JACLS-02 or JPLSG ALL-T11 protocol.[12–14] Other subtypes, including acute myeloid leukemia (AML), were primarily managed following contemporary Japanese protocols.

Diagnostic interval

This study mainly focused on the DI, defined as the duration of time from the onset of leukemic symptoms to the diagnosis of leukemia. To accurately gauge the DI, we categorized the diagnostic process into the following five components with reference to previous reports (Fig. 1)[2,15]: the patient interval (interval from the onset of leukemic symptoms to the patient's first medical contact), physician interval (interval from the first medical contact to diagnosis of leukemia), DI, treatment interval (interval from diagnosis of leukemia to initiation of

125 treatment), and total interval (interval from onset of leukemic symptoms to initiation of
126 treatment). The date of symptom onset was collected at the first admission through a
127 physician interview and recorded on the medical chart. We defined the date of diagnosis as
128 the date when a diagnostic bone marrow test was performed. The date of initiating treatment
129 was defined as the date when cancer-specific combination chemotherapy was initiated.
130 Initiation of supportive therapies such as hydration therapy, transfusion therapy, or
131 prophylactic antibiotic treatment was not defined as initiation of treatment for leukemia. All
132 intervals were measured in days.
133
134 *Study outcome*
135 The aim of our study was to determine whether a prolonged DI is associated with patient
136 survival. The primary outcomes were 5-year event-free survival (EFS) and 5-year overall
137 survival (OS). EFS was defined as the duration of time from diagnosis to relapse, death, or
138 last medical contact without relapse. OS was defined as the duration of time from diagnosis
139 to death or last medical follow-up. Relapse was defined as clinical or hematological
140 recurrence of leukemia. Non-relapse death was defined as death of any cause other than
141 relapse. Although death of relapse and non-relapse death were considered competing events,
142 non-relapse death was not observed in this cohort.
143

Statistical analysis

We described patients' characteristics and then calculated each interval, providing the median and interquartile range (IQR) across categories. The following categories were selected based on previous research, clinical significance, and data availability: sex, age at diagnosis, leukemic subtype, initial white blood cell count, initial platelet count, initial lactate dehydrogenase level, NCI classification, low-risk features with *ETV6::RUNX1* or hyperdiploidy, intensive care unit admission, hematopoietic stem cell transplantation, relapse or refractory disease, primary medical contact type, residence area, onset season, and period of diagnostic year. The initial white blood cell count, platelet count, and lactate dehydrogenase level were categorized using cutoffs of $5 \times 10^4/\mu L$, $5 \times 10^4/\mu L$, and 1000 U/L, respectively. The first medical contact type was distinguished between pediatrician and non-pediatrician. The residence area was grouped into Okayama prefecture and non-Okayama prefecture. Onset seasons were categorized as spring (March–May), summer (June–August), autumn (September–November), and winter (December–February). Probabilities of OS and EFS were calculated using Kaplan–Meier estimators.[16] Differences in survival were compared using the log-rank test.[17] We defined a DI of ≥30 days as a prolonged DI based on the IQR of our results. A sensitivity analysis was conducted by modifying the threshold from ≥30 days to ≥20 days. We compared the differences in survival as categorized by a prolonged physician interval, which excluded the patient interval from the DI. Additionally, we defined

a physician interval of >7 days as a prolonged physician interval. All statistical analyses were performed using EZR Version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[18] a graphical user interface for R Version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered statistically significant for all analyses.

Ethics statement

The patients or their parents gave opt-out consent in accordance with the Declaration of Helsinki. The study was approved by the institutional ethics committee of Okayama University (2203-034).

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. From 2007 to 2022, 103 children (72 boys, 31 girls) with leukemia were eligible for analysis. We divided our cohort into two groups of patients, those with ALL and those with non-lymphoid leukemia, with reference to previous studies.[5] We considered that the biological differences between ALL and non-lymphoid leukemia might contribute to variations in the diagnostic process. ALL comprised BCP-ALL, T-ALL/T-LL, Philadelphia chromosome-positive ALL, infant ALL, and Burkitt leukemia.

Patients with non-lymphoid leukemia included those with AML, chronic myeloid leukemia, and juvenile myelomonocytic leukemia. BCP-ALL was the most frequent subtype (n = 64, 62%), followed by AML (n = 13, 13%) and T-ALL/T-LL (n = 11, 11%). The clinical data for each individual child are shown in Supplemental Table S1. Nine (9%) patients required intensive care unit admission at the approximate time of initial treatment induction (the detailed clinical information is summarized in Supplemental Table S2).

Distribution of each interval

Table 2 shows the distribution of each interval by variables. The median DI was 20 days (IQR: 9–35 days) in patients with ALL and 14 days (IQR: 10–27 days) in patients with non-lymphoid leukemia (Supplemental Figure S1). Variables categorized by other factors such as intensive care unit admission, hematopoietic stem cell transplantation, relapse or refractory disease, first medical contact, residence area, onset season, and year of diagnosis are summarized in Supplemental Table S3. We also assessed the relationship between symptoms before diagnosis and each interval (Supplemental Table S4). Patients with bone or joint pain tended to have a prolonged DI (median DI: 26.5 days).

We measured the DIs of patients with BCP-ALL and patients with a good prognosis because we considered that patients with a good prognosis may have slower progression and a prolonged DI. In this analysis, we defined a good prognosis as the presence of BCP-ALL

with NCI-SR or low-risk ALL (with *ETV6::RUNX1* or hyperdiploidy). Patients with NCI-SR and those with low-risk ALL tended to have a longer DI than the other patients with ALL. The median DI was 25 days (IQR: 11.25–39.25 days) in children with low-risk ALL and 18 days (IQR: 9–31.5 days) in children in the other ALL groups.

Survival analysis

We assessed the relationship between the DI and patient survival. The median follow-up time among all patients was 2,366 days (IQR: 1171.5–3607 days). We observed 15 deaths (9 in children with ALL and 6 in children with non-lymphoid leukemia). The 5-year EFS was 75.0% in patients with ALL and 40.0% in patients with non-lymphoid leukemia, while the 5-year OS was 91.1% and 60.0%, respectively. Among patients with ALL, BCP-ALL had the best outcome with a 5-year EFS of 81.9% and 5-year OS of 98.1%. We found that a prolonged DI, which was defined as ≥30 days, was associated with neither 5-year EFS (70.1% for <30 days and 68.3% for ≥30 days, $P = 0.99$, log-rank test) nor 5-year OS (84.7% for <30 days and 89.4% for ≥30 days, $P = 0.85$, log-rank test) (Fig. 2A and B). This result was consistent even when restricted to children with ALL. The 5-year EFS and OS rates were not different between patients with ALL who had a prolonged DI and those with a standard DI (Fig. 2C and D). The survival of children with leukemia showed no significant difference when altering the threshold day for a prolonged DI from 30 to 20 days (Supplemental Figure

2). The physician interval, defined as the duration of time from the initial medical contact to the diagnosis of leukemia, was not associated with either the 5-year EFS (76.0% for ≤7 days and 62.9% for >7 days, $P = 0.23$, log-rank test) or 5-year OS (87.5% for ≤7 days and 84.8% for >7 days, $P = 0.64$, log-rank test) when defining a prolonged physician interval as >7 days (Supplemental Figure S3). Additionally, we compared a treatment interval of ≤5 versus >5 days according to previous reports.[19,20] A prolonged treatment interval was not associated with EFS in children with leukemia. The 5-year EFS was 72.7% at a treatment interval of ≤5 days and 61.9% at a treatment interval of >5 days ($P = 0.18$, log-rank test) (Supplemental Figure S4A). This result was also maintained in children with only ALL; the 5-year EFS was 75.3% at a treatment interval of ≤5 days and 74.6% at a treatment interval of >5 days ($P = 0.85$, log-rank test) (Supplemental Figure S4B). We focused on children with low-risk ALL (*ETV6::RUNX1* or hyperdiploidy) and found that those with a standard DI had excellent 5-year EFS compared with those with a prolonged DI (100% with a standard DI and 72.7% with a prolonged DI, $P = 0.033$) (Supplemental Figure S5).

Discussion

In this retrospective study, we measured the DI for a leukemia diagnosis and assessed the impact of a prolonged DI on survival in children with leukemia. A prolonged DI was not associated with poor survival in children with leukemia.

The intervals in our study are similar to those in previous studies on pediatric leukemia.[2,4,5] In our study, the median patient, physician, diagnostic, treatment, and total intervals were 4, 7, 20, 3, and 25 days, respectively. The largest Canadian observational study on the DI in childhood cancer reported that the median patient, physician, diagnostic, treatment, and total intervals for leukemia were 8, 3, 19, 1, and 21 days, respectively.[2] Although the patient interval was shorter in our cohort, the DI and total interval in our study are similar to those observed in the Canadian study. The patient interval was one of the longest time segments and was responsible for the interval-determining step of the total interval in the Canadian study.[2] The shorter patient interval in Japan may reflect differences in the medical and insurance systems between these two countries. In the largest systematic review, the median time to diagnosis of acute leukemia was approximately 3 weeks and was consistent across several studies.[5] However, our study showed that the DI was longer for lymphoid leukemia than for myeloid leukemia (median DI of 20 days and 14 days, respectively), which is different from the results of the systematic review.[5] This reversal in the results may be partially explained by the fact that the DI for myeloid leukemia in our cohort was shorter than the previously reported DI, although the limited number of patients in our cohort may have been associated with this outcome.

Several studies regarding the DI in pediatric cancer, encompassing various malignancies, showed that older age was associated with a prolonged DI.[1,2,5] However, in our cohort, the

median DI was shorter in the older age group (20 days for patients aged <6 years and 17.5 days for patients aged ≥6 years). This discrepancy might have arisen from the fact that our study used an age threshold of ≥6 years and included only patients with leukemia, whereas several other studies included older patients and those with heterogeneous cancers, such as sarcomas. Younger children tend to have low-risk ALL (*ETV6::RUNX1* and hyperdiploidy),[8,21,22] potentially explaining the different results in our cohort.

In this study, children who had BCP-ALL with NCI-SR or low-risk ALL (*ETV6::RUNX1* or hyperdiploidy) tended to have a prolonged DI. These trends may reflect biological differences, including the fact that ALL with *ETV6::RUNX1* and hyperdiploidy tends to exhibit slower progression.[21,22] In adult cancers, aggressive tumors reportedly tend to have a shorter symptomatic window, a phenomenon referred to as the "waiting time paradox."[1,2,5]

A prolonged DI was not associated with survival of pediatric leukemia in this study. Studies on the association between a delayed diagnosis and survival in pediatric leukemia are limited.[3–5,11] A recent Chinese retrospective study revealed a negative association of the DI with survival.[4] In a Canadian cohort study, the DI was not associated with survival of pediatric ALL.[11] In several retrospective studies of adults with AML, the relationship between the treatment interval and the prognosis was also analyzed,[19,23] and a recent study suggested that delayed initiation of treatment does not have a negative effect on survival.[20] In our study, the treatment interval was not associated with EFS (Supplemental Figure S3). Our

results may indicate that a prolonged DI does not directly imply a delay in diagnosis but instead reflects the biology of leukemia, including the feature of slower progression. Thus, the diagnosis is still considered timely even if the DI is prolonged. Waiting for the results of cytogenetic and genetic tests to stratify precise therapies may be appropriate.

In this retrospective study, we analyzed data from a single center; thus, the study has some limitations. First, we relied on data from the patients' electronic medical records. Therefore, we inevitably included some inaccuracy for each interval. However, our findings regarding the DI are similar to those of previous studies.[1,2,4,5] Second, the definition of symptom onset is a limitation of our study. The perceived timing of symptom onset depends on the children or their parents, rendering the patient interval less robust. However, the patient interval was shorter in our study, and we considered that the impact of measurement error was relatively small. Furthermore, the patient interval is a matter of concern for guardians, making it a clinically significant aspect of the diagnostic process. To address the limitation of the time-zero problem, we conducted additional analyses comparing the survival of children with ALL categorized by the physician interval. The physician interval was not associated with either the 5-year EFS or 5-year OS when the threshold for a prolonged physician interval was set at 7 days. Third, our sample size was small because our study was performed at a single center. Therefore, the analyses may have been underpowered, and differences in survival by the DI may not have been detected. Finally, our cohort included heterogeneous subtypes of pediatric

leukemia treated using different chemotherapy protocols during different periods of time. However, we were unable to perform a stratified analysis because of the limited number of patients. Therefore, our results should be interpreted with caution, and a larger nationwide study is warranted.

Conclusions

We retrospectively measured the DI of pediatric leukemia, and the median DI was 20 days. A prolonged DI (≥30 days) showed no association with the survival of children with leukemia. Our findings may suggest that a prolonged DI has a limited impact on the prognosis of children with leukemia.

Acknowledgments

We thank Ellen Knapp, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Funding Information

This work was supported by JSPS KAKENHI Grant Number JP23K14978 (Grant-in-Aid for Early-Career Scientists)

Authorship Contributions

All authors contributed to the study conception and design. K.T. wrote the manuscript. K.T., M.O., H.I., T.S., K.K., K.F., Y.T., and K.W. provided medical care for the patients. N.M. conducted the statistical review from an expert standpoint. K.W. and H.T. revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1 Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer: a review. *Cancer*. 2007;110:703–713.

2 Dang-Tan T, Trottier H, Mery LS, et al. Delays in diagnosis and treatment among children and adolescents with cancer in Canada. *Pediatr Blood Cancer*. 2008;51:468–474.

3 Baker JM, To T, Beyene J, et al. Influence of length of time to diagnosis and treatment on the survival of children with acute lymphoblastic leukemia: A population-based study. *Leuk Res*. 2014;38:204–209.

4 Dai Q, Liu R, Wang Y, et al. Longer Time Intervals From Symptom Onset to Diagnosis Affect the Overall Survival in Children With Acute Lymphoblastic Leukemia. *J Pediatr Hematol Oncol*. 2022;44:285–292.

5 Brasme J-F, Morfouace M, Grill J, et al. Delays in diagnosis of paediatric cancers: a systematic review and comparison with expert testimony in lawsuits. *Lancet Oncol*. 2012;13:e445–e459.

6 Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *N Engl J Med*. 2015;373:1541–1552.

7 Kato M, Manabe A. Treatment and biology of pediatric acute lymphoblastic leukemia. *Pediatr Int*. 2018;60:4–12.

8 Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. *Haematologica*. 2020;105:2524–2539.

9 Goldstick JE, Cunningham RM, Carter PM. Current Causes of Death in Children and Adolescents in the United States. *N Engl J Med*. 2022;386:1955–1956.

10 Pizzo PA and PDG. Principles and Practice of Pediatric Oncology. Seventh. New York: Lippincott Williams & Wilkins; 2015. 101–112 p.

11 Gupta S, Gibson P, Pole JD, et al. Predictors of diagnostic interval and associations with outcome in acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2015;62:957–963.

12 Takahashi Y, Ishida H, Imamura T, et al. JACLS ALL-02 SR protocol reduced-intensity chemotherapy produces excellent outcomes in patients with low-risk childhood acute lymphoblastic leukemia. *Int J Hematol*. 2022;115:890–897.

13 Koh K, Kato M, Saito AM, et al. Phase II/III study in children and adolescents with newly diagnosed B-cell precursor acute lymphoblastic leukemia: Protocol for a nationwide multicenter trial in Japan. *Jpn J Clin Oncol*. 2018;48:684–691.

14 Sato A, Hatta Y, Imai C, et al. Nelarabine, intensive L-asparaginase, and protracted intrathecal therapy for newly diagnosed T-cell acute lymphoblastic leukaemia in children and young adults (ALL-T11): a nationwide, multicenter, phase 2 trial

including randomisation in the very high-risk group. *Lancet Haematol*. 2023;10:e419–432.

15 Weller D, Vedsted P, Rubin G, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer*. 2012;106:1262–1267.

16 Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observationsorg. *J Amer Statist Assoc*. 1958;53:457-481.

17 Bland JM, Altman DG. The logrank test. *BMJ*. 2004;328:1073.

18 Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48:452–458.

19 Bertoli S, Bérard E, Huguet F, et al. Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia. *Blood*. 2013;121:2618–2626.

20 Röllig C, Kramer M, Schliemann C, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? *Blood*. 2020;136:823–830.

21 Haas OA, Borkhardt A. Hyperdiploidy: the longest known, most prevalent, and most enigmatic form of acute lymphoblastic leukemia in children. *Leukemia*. 2022;36:2769–2783.

22 Jeha S, Choi J, Roberts KG, et al. Clinical significance of novel subtypes of acute lymphoblastic leukemia in the context of minimal residual disease-directed therapy. *Blood Cancer Discov*. 2021;2:326–337.

23 Sekeres MA, Elson P, Kalaycio ME, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood*. 2009;113:28–36.

TABLE 1 Patients' characteristics

		ALL						non-lymphoid			
		BCP-ALL	T-ALL/LL	Ph-ALL	Infant-ALL*	Burkitt leukemia	**ALL total**	AML	CML	JMML	**non-lymphoid total**
Number of Patients		64	11	5	4	4	88	13	1	1	15
Sex(M/F)		42/22	10/1	5/0	2/2	3/1	62/26	8/5	1/0	1/0	10/5
Age (year)		5 [1 − 15]	9 [2 − 15]	5 [3 − 8]	0 [0 − 0]	8 [8 − 10]	5 [3 − 10]	7 [0 − 13]	8	0	7 [4.5 − 12]
Initial WBC count ($\times 10^9$/L)		8.86 [3.0175 − 25.3425]	151.170 [79.515 − 304.505]	86.870 [53.53 − 126.9]	427.800 [95.065 − 774.275]	9.180 [6.405 − 11.8125]	14.49 [4.8275 − 50.9875]	8.880 [5.36 − 31.55]	208.35	94.6	16.41 [5.715 − 50.915]
Initial Plt count ($\times 10^9$/L)		86 [44 − 178.3]	65 [49.5 − 139]	127 [48 − 162]	47.5 [40.5 − 59.5]	110.5 [44.5 − 174.5]	82.5 [44 − 175]	49 [15 − 77]	534	11	49 [14.5 − 81.5]
Initial LDH level		458.5 [313.25 − 893.5]	2,287 [1,115 − 3,025.5]	575 [330 − 1,295]	1,610 [1,371.75 − 2,219.25]	2,694 [2,489 − 3576.75]	580 [329.25 − 1590.75]	587 [411 − 822]	520	881	587 [415 − 851]
CNS disease	**positive**	1	2	2	1	1	7	1	0	0	1
	negative	63	9	3	3	3	81	12	1	1	14
ICU admission	**Yes**	1	5	0	1	1	8	0	0	1	1
	No	63	6	5	3	3	80	13	1	0	14
HSCT	**Yes**	9	2	5	2	2	20	8	0	0	8
	No	55	9	0	2	2	68	5	1	1	7
diagnosis before 2015	**Yes**	38	4	3	2	3	50	7	0	0	7
	No	26	7	2	2	1	38	6	1	1	8
alive	**Yes**	61	9	4	3	2	79	8	1	0	9
	No	3	2	1	1	2	9	5	0	1	6

Data are shown as n or median (interquartile range).

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCP, B-cell precursor; CML, chronic myeloid leukemia; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; JMML, juvenile myelomonocytic leukemia; LDH, lactate dehydrogenase; LL, lymphoblastic lymphoma; Ph, Philadelphia chromosome-positive; Plt, platelet; WBC, white blood cell.

*All infants with ALL had *KMT2A* rearrangement.

TABLE 2 Intervals in days according to each variable

	Number of patients (%)	Patient interval	Physician interval	Diagnostic interval	Treatment interval	Total interval
Overall	103 (100%)	4 [0 – 16]	7 [4 − 18]	20 [9.5 − 33.5]	3 [1 − 6]	25 [13 − 39]
ALL	88 (85%)	4 [0 – 17]	7 [4 – 18.25]	20 [9 – 35]	3 [1 – 6]	24 [12 – 38.5]
non-lymphoid leukemia	15 (15%)	4 [1 – 10.5]	10 [3 – 13]	14 [10 – 27]	4 [3 – 7]	27 [16 – 37.5]
Sex						
Male	72 (70%)	4 [0.75 – 15]	7 [3.75 – 18]	19 [9 – 32]	3 [1 – 6.25]	22 [12 – 38]
Female	31 (30%)	2 [0 – 20.5]	8 [4.5 – 19]	22 [12.5 – 36]	4 [1 – 5]	26 [15 – 41]
Age group						
< 6	51 (50%)	4 [1 – 17.5]	8 [4 –18.5]	20 [12 – 36]	4 [1 – 6.5]	26 [15 – 42.5]
≥ 6	52 (50%)	3.5 [0 – 13.5]	6 [3 – 14.25]	17.5 [8.75 – 31.25]	3 [1 – 5.25]	22.5 [11.75 – 33.25]
Leukemia subtypes						
BCP-ALL	64 (62%)	4 [0 – 16.75]	7.5 [4 – 20.5]	24 [9.75 – 36]	4 [2 – 6]	30 [13 – 41]
T-ALL/LL	11 (11%)	4 [1 – 13.5]	7 [3.5 – 9.5]	12 [8.5 – 16.5]	1 [0.5 – 1]	14 [9 – 19]
Ph-ALL	5 (4.9%)	2 [1 – 8]	18 [8 – 19]	19 [16 – 45]	2 [1 – 6]	25 [17 – 46]
infant-ALL	4 (3.9%)	16 [10.75 – 20]	4 [2.5 – 5.25]	20.5 [15.5 – 23.5]	1 [0.75 – 1]	21.5 [16.50 – 24.25]
Burkitt leukemia	4 (3.9%)	8 [2.25 – 14]	7.5 [2.25 – 17]	22.5 [12.75 – 29.75]	1.5 [1 – 3]	24 [15.75 – 30.75]
AML	13 (13%)	3 [1 – 8]	11 [4 – 13]	14 [10 – 28]	4 [3 – 7]	18 [15 – 33]
Initial WBC count						
$< 5\times10^4$ /μL	76 (74%)	4 [0 – 15]	8 [4 – 20.5]	23.5 [10 – 35.25]	4 [3 – 6.25]	30 [14 – 41]
$\geq 5\times10^4$ /μL	27 (26%)	4 [1 – 18]	6 [3.5 – 10.5]	16 [8.5 – 22.5]	1 [1 – 3]	19 [9 – 27.5]
Initial Plt count						
$> 5\times10^4$ /μL	65 (63%)	4 [0 – 17]	9 [5 – 19]	21 [12 – 36]	3 [1 – 6]	27 [15 – 41]
$\leq 5\times10^4$ /μL	38 (37%)	4.5 [1 – 13]	4.5 [3 – 12.75]	14 [7.25 – 31]	3 [2 – 6]	19.5 [11.25 – 37.5]
Initial LDH level						
< 1000 U/L	69 (67%)	2 [0 – 15]	8 [4 – 20]	23 [10 – 35]	4 [3 – 6]	30 [15 – 41]
≥ 1000 U/L	34 (33%)	7 [2.25 – 17]	5.5 [3 – 10.75]	15 [9 – 28]	1 [1 – 3]	17.5 [12 – 30.75]
NCI classification						
NCI-SR ALL	43	4 [0 – 15]	8 [4 – 22.5]	24 [10.5 – 41]	4 [3 – 6.5]	30 [14 – 44]
Other-ALL	45	4 [1 – 17]	6 [3 – 12]	19 [9 – 29]	1 [1 – 4]	20 [9 – 33]
Low-risk classification						

low-risk ALL	30	3.5 [0 – 26.5]	8 [4 – 19.75]	25 [11.25 – 39.25]	5 [3 – 6]	31 [15.25 – 43]
non low-risk ALL	58	4 [1 – 14.5]	7 [3.25 – 17.25]	18 [9 – 31.5]	2 [1 – 5]	20 [12 – 33]

Data are shown as n, n (%), or median (interquartile range).

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCP, B-cell precursor; LDH, lactate dehydrogenase; LBL, lymphoblastic lymphoma; Plt, platelet; WBC, white blood cell.

†Low risk represents genetic features with *ETV6::RUNX1* or hyperdiploidy.

Figure legends

Fig. 1 Conceptive illustration of each time point and interval from the onset of symptoms to the initiation of treatment in this study. HCP, health care professionals

Fig. 2 Comparison of EFS and OS between patients with a long DI and those with a standard DI. We defined a long DI as ≥30 days. (A) EFS of children with leukemia. (B) OS of children with leukemia. (C) EFS of children only with ALL. (D) OS of children only with ALL. ALL, acute lymphoblastic leukemia; DI, diagnostic interval; EFS, event-free survival; OS, overall survival

Supplemental Figure S1. Dot plots represent the distributions of the (A) patient interval, (B) physician interval, (C) diagnostic interval, and (D) treatment interval in our cohort.

Supplemental Figure S2. Comparison of EFS and OS between patients with a prolonged DI and those with a standard DI. We defined a prolonged DI as ≥20 days. (A) EFS of children with leukemia. (B) OS of children with leukemia. (C) EFS of children only with ALL. (D) OS of children only with ALL. ALL, acute lymphoblastic leukemia; DI, diagnostic interval; EFS, event-free survival; OS, overall survival.

Supplemental Figure S3. Comparison of EFS and OS between patients with a prolonged PI and those with a standard PI. We defined a prolonged PI as >7 days. (A) EFS of children with leukemia. (B) OS of children with leukemia. (C) EFS of children only with ALL. (D) OS of children only with ALL. ALL, acute lymphoblastic leukemia; PI, physician interval; EFS, event-free survival; OS, overall survival.

Supplemental Figure S4. Comparison of EFS stratified by a TI of 0–5 days or longer. (A) EFS of children with leukemia and (B) EFS of children with ALL. ALL, acute lymphoblastic leukemia; EFS, event-free survival; TI, treatment interval.

Supplemental Figure S5. (A) Comparison of EFS between low-risk patients with ALL and a standard DI and those with a prolonged DI. (B) Comparison of EFS between non-low-risk patients with ALL and a standard DI and those with a prolonged DI. We defined a prolonged DI as ≥30 days. ALL, acute lymphoblastic leukemia; DI, diagnostic interval; EFS, event-free survival.

Supplemental Table S1. Summary of available clinical information of study cohort. HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LDH, lactate dehydrogenase; Plt, platelet; WBC, white blood cell. *0, absence of symptom; 1, presence of

symptom. †0, spring (March–May); 1, summer (June–August); 2, autumn (September–November); 3, winter (December–February). ‡0, inside Okayama prefecture; 1, outside Okayama prefecture. ¶0, pediatrician; 1, non-pediatrician; 2, data unavailable. **0, Yes; 1, No.

Supplemental Table S2. Clinical details of patients who needed ICU admission around treatment induction. ALL, acute lymphoblastic leukemia; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CHDF, continuous hemodiafiltration; Cre, creatinine; F, female; ICU, intensive care unit; JMML, juvenile myelomonocytic leukemia; K, potassium; LDH, lactate dehydrogenase; M, male; P, phosphorus; T-ALL/T-LL, T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma; TLS, tumor lysis syndrome; UA, uric acid; WBC, white blood cell.

Supplemental Table S3. Intervals in days according to each variable. Data are shown as n, n (%), or median (interquartile range). HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit.

Supplemental Table S4. Relationships between symptoms and intervals. Data are shown as n, n (%), or median (interquartile range).

58