Comparison of myelosuppression using the D-index between children and adolescents/young adults with acute lymphoblastic leukemia during induction chemotherapy

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August 7, 2020

Abstract

Background. Adolescents/young adults (AYAs) with acute lymphoblastic leukemia (ALL) are more likely to have chemotherapy-related complications than children. In addition, several reports have shown that infections account for most of the therapy-related mortality during cancer treatment in AYAs. Thus, we hypothesized that chemotherapy-induced myelosuppression is more severe in AYAs than in children, and the state of neutropenia was compared between children and AYAs using the D-index, a numerical value calculated from the duration and depth of neutropenia. *Procedure.* This study retrospectively analyzed 95 patients newly diagnosed with ALL at our institution between 2007 and 2019. Of these, 81 were children (< 15 years old) and 14 were AYAs ([?] 15 years old). The D-index and duration of neutropenia during induction chemotherapy for ALL were compared between children and AYAs. *Results.* The median D-index of children was significantly higher than that of AYAs (8,187 vs. 6,446, respectively, P = 0.017). Moreover, the median duration of neutropenia was also significantly longer in children than in AYAs (24.0 days vs. 11.5 days, respectively, P = 0.007). *Conclusion.* Contrary to our expectations, myelosuppressive toxicity during induction chemotherapy for ALL was more severe in children than in AYAs.

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Abstract word count: 193

Main text word count: 2,120

Tables: 2

Figures: 2

Short running title: Comparison of myelosuppression between children and AYAs

Key words: acute lymphoblastic leukemia, adolescents and young adults, chemotherapy, D-index, myelosuppression.

Abbreviations Key

Abbreviations Full term

AYAs adolescent and young adults

ALL acute lymphoblastic leukemia

BCP-ALL precursor B-cell acute lymphoblastic leukemia

BFM Berlin-Frankfurt-Münster

EZR Easy R

FN febrile neutropenia

HR high-risk

IFI invasive fungal infection

IR intermediate-risk

TRM therapy-related mortality

WBC white blood cell

Abstract

Background. Adolescents/young adults (AYAs) with acute lymphoblastic leukemia (ALL) are more likely to have chemotherapy-related complications than children. In addition, several reports have shown that infections account for most of the therapy-related mortality during cancer treatment in AYAs. Thus, we hypothesized that chemotherapy-induced myelosuppression is more severe in AYAs than in children, and the state of neutropenia was compared between children and AYAs using the D-index, a numerical value calculated from the duration and depth of neutropenia. Procedure. This study retrospectively analyzed 95 patients newly diagnosed with ALL at our institution between 2007 and 2019. Of these, 81 were children ($<$ 15 years old) and 14 were AYAs ([?] 15 years old). The D-index and duration of neutropenia during induction chemotherapy for ALL were compared between children and AYAs. Results. The median D-index of children was significantly higher than that of AYAs (8,187 vs. 6,446, respectively,$P = 0.017$). Moreover, the median duration of neutropenia was also significantly longer in children than in AYAs (24.0 days vs. 11.5 days, respectively, $P = 0.007$). Conclusion. Contrary to our expectations, myelosuppressive toxicity during induction chemotherapy for ALL was more severe in children than in AYAs.

Key words: acute lymphoblastic leukemia, adolescents and young adults, chemotherapy, D-index, myelosuppression.

Introduction

Clinical outcomes of treatment for acute lymphoblastic leukemia (ALL) in children have greatly improved over the past decades due to the identification of effective methods for administration of chemotherapeutic agents, the introduction of risk-stratified protocols, and the development of supportive care [1-3]. The use of a pediatric protocol for the treatment of adolescents/young adults (AYAs) with ALL has proven to be more effective than the regimen used for adult patients with ALL [4-5]. However, it has been suggested that applying a pediatric protocol for ALL to AYAs can lead to an increased rate of therapy-related toxicities [6-7]. In addition, several studies have demonstrated that AYAs exhibit higher morbidity than children during treatment for ALL, and some reports have shown that infections account for the majority of therapy-related

mortality (TRM) in AYAs [8-13]. Furthermore, the incidence of invasive fungal infection (IFI) during cancer chemotherapy is higher in AYAs than in children [14-16]. A possible explanation for these issues is the difference in chemotherapy-induced myelotoxicity between children and AYAs. Thus, we aimed to test this hypothesis in the present study.

To accurately determine the intensity of myelosuppression, a numerical value called the D-index, which is based on the duration and depth of neutropenia, was employed. The D-index was developed as a tool to predict the risk of invasive fungal infections (IFI), and showed better performance than simply utilizing the duration of neutropenia as a predictor of IFI [17,18]. Further, it is easily calculated using only the absolute neutrophil counts during chemotherapy. Therefore, the D-index is considered to be a useful and effective clinical parameter to assess myelosuppressive toxicity.

Methods

Study design

This study targeted patients who underwent induction chemotherapy for ALL at the Department of Hematology/Oncology for Children and Adolescents, Sapporo Hokuyu Hospital, between April 2007 and December 2019. Children and AYAs were defined as < 15 years of age and [?] 15 years of age, respectively. Analyses were conducted based on all data obtained up to February 31, 2020.

A total of 115 patients were treated at our institution according to the Japanese protocols for ALL, which are based on the Berlin-Frankfurt-Munster (BFM) regimen [19]. Two protocols were adopted to treat the patient with precursor B-cell ALL (BCP-ALL), and all of the enrolled patients underwent 7 days of prephase with steroid and one intrathecal dose of methotrexate, followed by the induction therapy. The patients then received 4 chemotherapeutic agents consisting of vincristine, daunorubicin, L-asparaginase, prednisolone, and intrathecal chemotherapy during the induction. In the protocols used until December 2012, the patients stratified into the intermediate-risk (IR) or high-risk (HR) groups were given an additional dose of cyclophosphamide (1,200 mg/m^2/dose). Similarly, those who were classified into IR or HR after 2013 received two additional doses of daunorubicin (25 mg/m^2/dose). The treatment regimens for IR and HR were the same in each protocol. As for the risk-stratifying method during the induction therapy, the two protocols in this analysis applied the same approach conventionally used in the BFM-typed regimen, in which patients with ALL were stratified according to National Cancer Institute criteria [20], cytogenetic abnormalities, response to the prephase and blast counts of bone marrow at day 15. In addition, patients with T-cell ALL and mixed-phenotype ALL were treated with the same regimen as the IR/HR protocol for BCP-ALL during the induction therapy. Details of the protocols are shown in Table I.

Of the enrolled patients, 5 infant patients with ALL, one patient with mature B-cell ALL, and one patient with Philadelphia chromosome-positive ALL who received different types of chemotherapy were excluded from this study. Furthermore, one patient with trisomy 21, one patient who started tyrosine kinase inhibitor (TKI) during induction therapy, 3 patients who had already been administered prednisolone at the time of hospitalization, and 4 patients who had not completed all scheduled anti-cancer agents for the induction were excluded. Additionally, two patients who died during induction chemotherapy and two patients who did not achieve complete remission before starting an early intensification therapy were also excluded. Therefore, a total of 95 patients were defined as eligible for the present analyses. Of these, 81 were children and 14 were AYAs. The median age of the children at diagnosis was 5.7 years old (1.3-14.7 years old), and that of the AYAs was 16.9 years old (15.1-24.0 years old). Further details regarding the characteristics of the patients are shown in Table II. No significant differences were found in the patients' gender, immunophenotypes, or cytogenetic abnormalities except for WBC counts at diagnosis and M3 marrow at day 15.

The neutropenic episodes (neutrophil counts $< 0.5 \times 10^9$/L) of the analyzed patients were retrospectively investigated, and the D-index was calculated from the duration and depth of the neutropenia. Then, the D-index and the duration of neutropenia in the induction course were then statistically compared between children and AYAs.

Finally, the incidence rates of FN, bacteremia, and IFI were surveyed in the eligible patients and were compared between children and AYAs. The incidence rate was defined as the number of newly identified infectious complications per whole number of accomplished induction chemotherapies. Blood cultures were always conducted whenever patients experienced FN at the institution, and any positive result from the cultures was considered to be bacteremia. IFI was defined according to the standardized definitions of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycosis Study Groupconsensus group [21]. Antibacterial agents were not administered until the patients exhibited fever or some sign of infection, and granulocyte colony-stimulating factor was not used in all analyzed patients. In terms of the method to prevent infections, trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*pneumonia, and oral fluconazole at 10 mg/kg/day was used for all enrolled patients.

The present study was approved by the Institutional Review Board of Sapporo Hokuyu Hospital.

Definition and calculation of the D-index

The D-index is derived by plotting the absolute neutrophil count during neutropenia (< 0.5 x 10^9/L) and calculating the area over the curve, which is the difference of the expected neutrophil area (A_e) minus the area under the curve or A_0. A_e is calculated as the product of 500 and the number of days during which neutrophil counts are at or below the level of neutropenia. For instance, if a patient experienced 6 days of neutropenia, A_e is 3,000 (6x500) days * neutrophils/μL. A_0 is calculated using the trapezium rule, as follows:

$$A_0 = \sum_{\mathbf{i}=2}^{n} (t_i - t_{i-1}) \frac{N_{i-1} + N_i}{2}$$

Here, (t_i–t_{i-1}) is the time interval (days) between two consecutive neutrophil counts, and $N_i$and N_{i-1} are the respective neutrophil counts (per microliter) at times t_i and t_{i-1}. All available neutrophil counts are included in the calculation of the D-index, where the total number of neutrophil counts is n[17].

Statistical analyses

Fisher's exact test was used to compare categorical variables of the patients' baseline characteristics, and the incidence of infectious complications. The Mann-Whitney U test was used to compare continuous variables of the D-index and the period of neutropenia. A p- value of 0.05 or less was considered statistically significant. All statistical analyses were performed with EZR, which is a graphical user interface for R (The R Foundation for Statistical Computing). More precisely, it is a modified version of the T commander designed to add statistical functions frequently used in biostatistics [22].

Results

The median D-index of the children was significantly higher than that of the AYAs (8,187, range, 0-20,095 vs. 6,446, range, 0-10,532, respectively, $P = 0.017$) (Figure 1). Similarly, the median duration of neutropenia was also significantly longer in children than in AYAs (24.0 days, range, 0-59 days vs. 11.5 days, range, 0-36 days, respectively, $P = 0.007$) (Figure 2). In terms of infectious complications during induction chemotherapy for ALL, FN occurred in 53.7% of the analyzed patients, with 55.6% in children and 42.9% in AYAs; however, the incidence of FN was not statistically different between the two groups ($P = 0.401$). Moreover, bacteremia and IFI were observed in 9.5% and 2.1% of the analyzed patients, respectively. These incidences were also not significantly different between children and AYAs (bacteremia: 8.6% vs. 14.3%, respectively, $P = 0.617$, IFI: 1.2% vs. 7.1%, respectively, $P = 0.274$).

Discussion

We conducted this retrospective study to elucidate the cause of the higher incidence of infection-related TRM in AYAs during chemotherapy for ALL compared with children. It has been presumed that the intensity of myelosuppression is more severe in AYAs, resulting in a considerable rate of infectious complications.

Generally, myelosuppressive toxicity is largely influenced by the types and doses of drugs used in the regimen, underlying diseases, and patient condition. Therefore, this study was limited to examining myelosuppression during induction chemotherapy for patients newly diagnosed with ALL. Usually, AYAs with ALL tend to have more enhanced therapies compared to children, as they are classified into a relatively high-risk group due to their age. In fact, all of the AYAs in this study received an additional dose of cyclophosphamide or two doses of daunorubicin, while more than half of the children did not receive these treatments. This difference was at first thought to contribute to increasing the susceptibility of AYAs to the myelosuppressive side effects to a greater extent than what is seen in children. However, contrary to our expectations, the D-index, which represents the state of neutropenia during chemotherapy for ALL, was significantly lower in AYAs than in children. This indicates that AYAs with ALL showed less profound neutropenia than children during the induction therapy for ALL. A study conducted at St. Jude Children's Research Hospital showed that young age (1-9.9 years old), compared to age [?] 10 years old, was associated with a significantly longer duration of neutropenia in all phases of chemotherapy for ALL [23]. Our present results support this argument. In this respect, it should be noted that our study has an advantage in assessing the neutropenic state using the D-index, since the duration of neutropenia does not reflect how neutrophil counts change during chemotherapy. Although some studies have assessed the myelosuppressive state using neutropenic duration or presence of anemia or thrombocytopenia, this is the first attempt to estimate the intensity of myelosuppression using the D-index. Given that the D-index allows an accurate evaluation of the neutropenic state, it is highly possible that children with ALL suffer from more profound chemotherapy-induced myelosuppression than AYAs.

One of the possible factors why AYAs experience less myelosuppressive toxicity could be due to the maximum dose of vincristine utilized. The enrolled patients were administered 1.5 mg/m^2/dose of vincristine, and its maximum dose was 2.0 mg. Thus, patients with body surface area > 1.33m^2, values typically observed in AYAs, will receive a lower dose of vincristine in the protocols. However, the myelotoxicity of vincristine is relatively weak [24]. Therefore, the smaller vincristine dose in AYAs seems to have a low impact on the present results. The mechanism causing differences in the myelosuppressive state between patients is considered to be multifactorial. In terms of body structure, children and AYAs are not the same, and individual organs mature rapidly during puberty, possibly affecting the distribution and metabolism of chemotherapeutic agents [25].

The results of the present study suggested that factors other than myelosuppression contribute to the higher incidence of infectious TRM in AYA. We previously investigated the reduced efficacy of antibiotic therapy for AYA neutropenic patients due to the relatively lower dose of antibiotics per body weight [26]. Moreover, non-infectious complications, which may subsequently lead to infection-related mortality or morbidity, have been observed more often in AYAs than in children [27-30]. In fact, sarcopenia during chemotherapy in children with a hematologic malignancy was reported as a possible risk factor for IFI [31]. Continued studies of these issues could indicate potential approaches to reduce the infectious TRM in AYAs with cancer.

This study has several limitations. First, the sample size of AYAs was relatively small compared that of children. However, equal variance of the two groups was confirmed, and the result was statistically significant. Therefore, it is conceivable that the results would be consistent with the present observations if the number of cases was increased. Second, regarding the infectious complications such as bacteremia and IFI during induction, their incidences were both apparently higher in AYAs than in children, though no significant differences were observed. This lack of statistical difference could be due to the low absolute number of infectious complications in this study. Moreover, there have been several reports that older age and treatment intensity were risk factors for severe infectious adverse events during the treatment for ALL [32-35].

In conclusion, myelosuppressive toxicity during induction chemotherapy for ALL appeared to be more severe in children than in AYAs, despite the relatively intensified treatment for AYAs. This suggests that factors other than myelosuppressive toxicity contribute to the vulnerability of AYAs with ALL to infectious mortality and morbidity. A similar study with other chemotherapeutic regimens should be pursued.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Legends

Figure 1.

Comparison of the D-index between children and AYAs

Figure 2.

Comparison of the duration of neutropenia between children and AYAs

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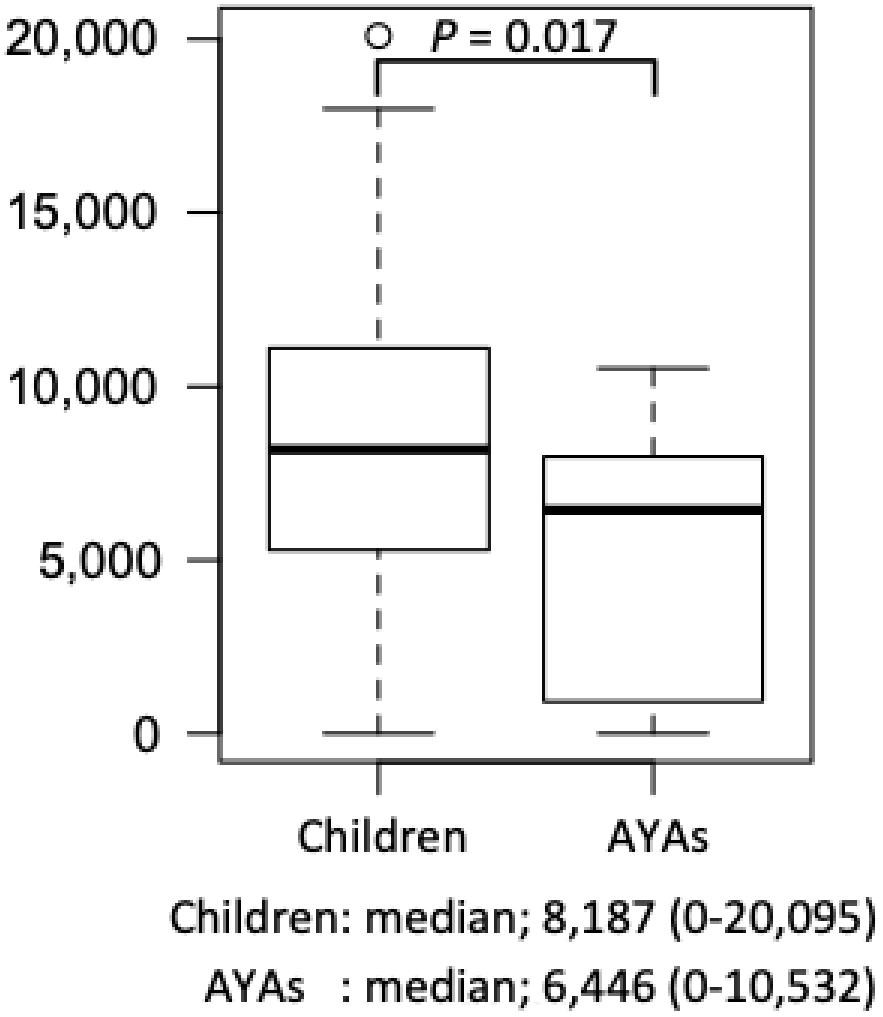

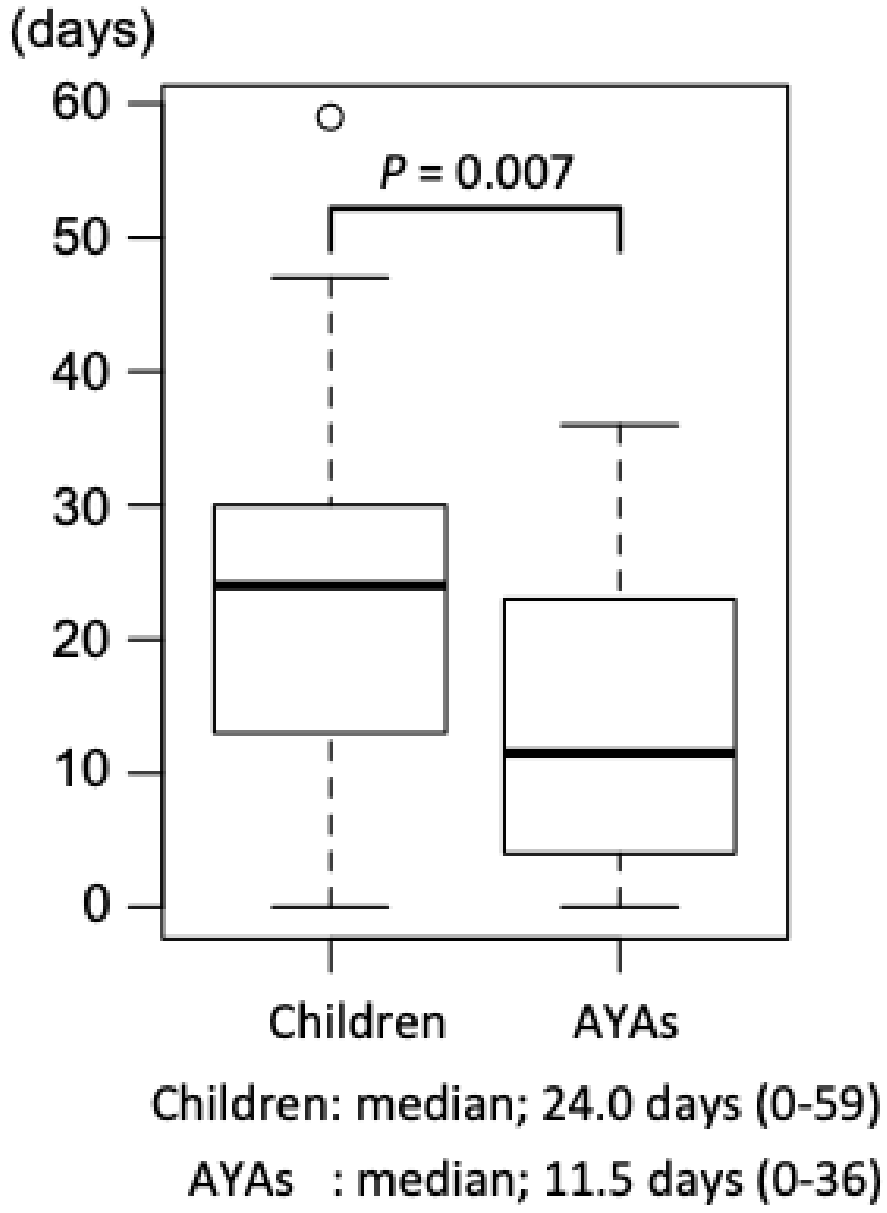

Children: median; 24.0 days (0-59)

AYAs : median; 11.5 days (0-36)