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Chemotherapy delays in children with acute lymphoblastic leukemia might influence the outcome of treatment

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is one of the most commonly occurring cancers among children with one of the highest survival rates, thanks to its very strict treatment protocol. In this paper, the impact of delays in treatment during the induction phase was assessed.

Material and methods: Retrospective single center analysis of 127 patients treated between years 2003 and 2015 was performed. Patients were categorized by their respective gender, age, leukemia variant, risk group and chemotherapy protocol used. The delays were measured using protocol milestones as reference points. The associations between treatment delay intervals and event-free survival (PFS) or overall survival (OS) were evaluated using Kaplan-Meier curves and univariate Cox proportional hazards regression models.

Results: Delays in treatment which occurred before the 8th day were associated with a 30% increase in the risk of death ($p < 0.01$) and a 33% increase in the risk of relapse or death ($p < 0.01$). The influence of delays after the 8th day was statistically insignificant. Delays were proven to have the most influence on outcome in the high-risk group, especially before the 8th day.

Conclusions: The ALL treatment protocols should be strictly followed as any delay may lead to worse patients' survival.

Key words: acute lymphoblastic leukemia, delays, oncology, hematology

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Introduction

Leukemias are one of the most commonly occurring types of neoplasms among children that account for about 30% of oncological diagnoses among pediatric patients. Out of all bone marrow derived neoplasms, acute lymphoblastic leukemia (ALL) is the most widespread type, occurring in 80% of patients suffering from leukemias. It also belongs to one of the most efficiently combated cancers, with 5-year survival rates nearing 90% [1]. Such efficiency can be contributed to rapid development of chemotherapy protocols, which have been constantly improved since their introduction in 1960s. Although different hospitals use different protocols, they share common core characteristics. A broad spectrum of chemotherapeutic agents is utilized, their administration is governed by a very strict time schedule and their dosage is adjusted depending on each patient's individual variables.

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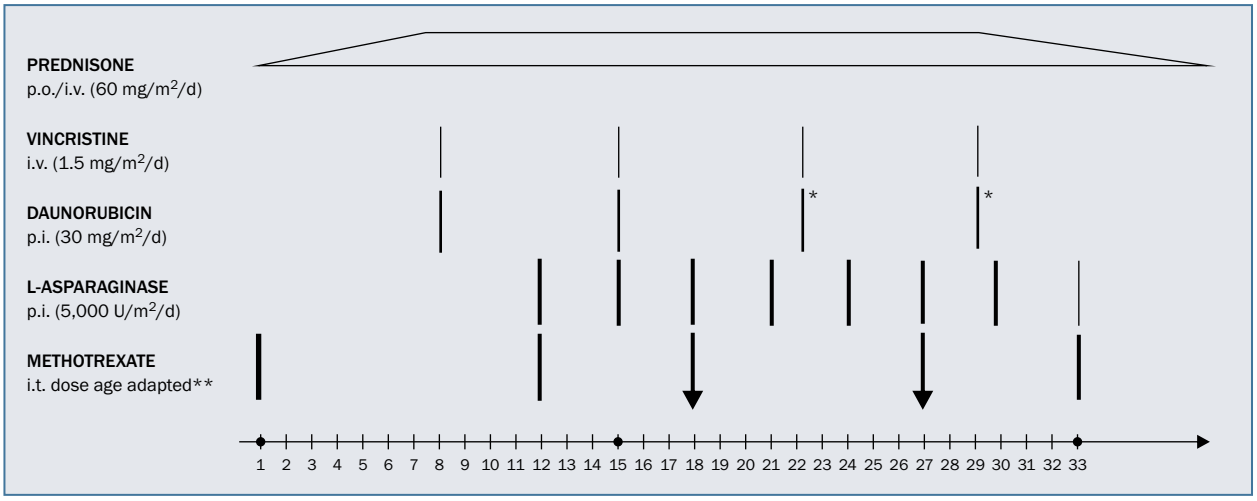

Figure 1. ALLIC BFM 2009 induction protocol, as taken from the official Berlin–Frankfurt–Munster Group Final Version of Therapy Protocol from August 14, 2009. The lines indicate the days of drug administration; *in case of standard risk (SR) T-cell acute lymphoblastic leukemia (T-ALL) and intermediate risk (IR) or high risk (HR) ALL additional doses of daunorubicin are administered on days 22 and 29. The days of bone marrow biopsies were marked with a dot on days 1, 15 and 33. Prednisone is given in 3 single doses per day, began with a total or 25% of the calculated dose, depending on clinical condition of the child, and increased rapidly considering laboratory findings, clinical response and diuresis. The withdrawal of prednisone should be started on the 29th day and last 9 days; **methotrexate (MTX) dose is age-adapted and given as follows: 6 mg for children <1 yo, 8 mg ≥1 and <2 yo, 10 mg ≥2 and <3 yo and 12 mg when the child is 3 years old or older. In case of central nervous system involvement or presence of blasts in the cerebrospinal fluid or traumatic lumbar puncture additional MTX is administered on days 18 and 27; p.o. — per os; i.v. — intravenous; p.i. — per infusionem; i.t. — intrathecal

ALLIC BFM (Berlin–Frankfurt–Munster) chemotherapeutic protocol from year 2002 and its improved version from year 2009 both consist of three main blocks of treatment: remission induction, consolidation and maintenance with the first phase, responsible for forcing the disease into remission, being the most intensive one [2]. The first 33 days of treatment protocol, shown in Figure 1, are decisive in the process of risk group stratification and play a crucial role in further prognosis. It has long been known that early treatment response, in particular the response to the prednisone prophase (absolute blast count on day 8, after 7 days of prednisone and one dose of intrathecal methotrexate) is one of the strongest independent prognostic factors of treatment outcome and has been extensively analyzed [3–5]. However, the effect of treatment delay in the early phases of the protocol on survival has not received enough attention [6]. It has been reported that the abandonment of therapy and treatment-related mortality is especially high in resource-poor settings [7, 8]. While, the rates of abandonment of therapy or toxic deaths are low in high-income countries [9]. Thus, treatment delay is believed to be one of the major contributors to inferior outcomes in low-income countries. In the light of these reports, the aim of this research was to assess the influence of treatment delay during the beginning of the induction phase of ALLIC BFM 2002 and 2009 protocols on the outcome of treatment. Finally, we compared ALLIC BFM 2002 and 2009 protocols.

Materials and methods

This retrospective analysis included children suffering from ALL treated at the single pediatric oncology center between 2003 and 2015. All patients diagnosed with both T-cell ALL (ALL-T) and B-cell ALL (ALL-B) treated with ALLIC BFM 2002 and ALLIC BFM 2009 protocols were included in the study. Clinical data were obtained from hospital records and assessed retrospectively. Treatment protocol, age of onset, sex, leukemia variant, prognostic risk group [standard risk (SR), intermediate risk (IR) and high risk (HR)], date of diagnosis, date of progression or relapse and date of last follow-up were identified.

In order to assess delay in treatment we used established protocol milestones, which represent the crucial days of protocol treatment. The 1st day of treatment, the measurement of steroid resistance from peripheral blood on the 8th day and the bone marrow biopsies on the 15th and the 33rd day were regarded to be the pivotal points in treatment regimens and are crucial in the process of risk group stratification. The expected dates of treatment corresponding to the 8th, 15th and 33rd days of the protocol were determined on the grounds of the 1st day of treatment and compared with the actual dates taken from hospital records. The intervals between the expected dates of the protocol milestones and the actual dates were calculated. Treatment delay has been defined as any delay that occured between protocol checkpoints that has not already been registered earlier.

Based on assumption testing, study group description and intragroup association were conducted using chi^2 and U Mann-Whitney tests as well as Spearman's rank correlation coefficient. Associations between prognostic risk groups were declared using Kruskal–Wallis one-way analysis of variance. As all the analyses were preplanned, no correction for multiple comparisons was applied.

The log-rank test was used to compare the survival of two subgroups — patients with and without at least 1-day delay in treatment protocol as well as between protocols. Finally, the associations of treatment delay intervals with the event-free survival (EFS) and overall survival (OS) were evaluated using Kaplan-Meier curves and univariate Cox proportional hazards regression modelling. EFS and OS were calculated from date of diagnosis to date of first event. Regarding EFS the event was defined as relapse or death and regarding OS — death as a result of any cause. The observation time was ceased at last follow-up if no event occurred. All calculations were performed using R. Significance level was set to p-value less than 0.05.

In order to establish whether the poorer prognosis in treatment occurs due to the delays or because of the already present adverse conditions, we divided the control group according to risk groups patients belonged to at the onset of treatment (high risk, intermediate risk, standard risk) and evaluated the associations of treatment delays with OS and EFS within these groups. We have also analyzed the reasons for treatment delay when found in patients' documentation, in particular adverse conditions.

Finally, we tried to determine whether delay at any point of the induction phase of the treatment protocol had impact on the risk of death and the risk of relapse or death in the analyzed group of children. In order to authenticate our analysis we compared the delayed and non-delayed groups in search of any comorbid factors that may influence our analysis and to see if the groups are comparable.

Table I. Group characteristics

Characteristics	Number or median	Percentage (if applicable) [%]
Median age [years]	5 (IQR: 2.73–10.39)	
Sex:		
• girls	52	40.94
• boys	75	59.06
Risk group:		
• SR	28	22.05
• IR	68	54.54
• HR	31	24.41
Leukemia variant:		
• T-ALL	17	13.39
• BCP-ALL	110	86.61
Steroid response:		
• good steroid response	118	92.91
• poor steroid response	9	7.09
Median WBC at day 1 [/μL]	12,870 (IQR: 4,890–43,425)	
OS	84.8% (95% CI: 78.4–91.6%)	
EFS	82.1% (95% CI: 75.3–89.5%)	
Median follow-up time	5.25 (IQR: 2.09–7.82)	

IQR — interquartile range; SR — standard risk; IR — intermediate risk; HR — high risk; T-ALL — T-cell acute lymphoblastic leukemia; BCP-ALL — B-cell precursor acute lymphoblastic leukemia; WBC — white blood cells; OS — overall survival; EFS — event-free survival

Results

One hundred twenty-seven children, treated at the Department of Pediatrics, Oncology and Hematology between 2003 and 2015, were included in this analysis. The detailed characteristics of the study group were presented in Table I.

In the study group, median age of diagnosis was 5 years (interquartile range: 7.66 years) and was equal in both girls and boys (p = 0.53). Although the protocol was updated during the time of the study, the group of patients after and prior to the update of 2009 were similar in terms of all clinical characteristics (p >0.05).

Eighty children were treated using ALLIC BFM 2002 (group 2002) and forty-seven using ALLIC BFM 2009 (group 2009). The delays occurred in 84 cases (61.3%) out of which 56 in group 2002 and 28 in the group 2009. Median overall protocol delay was equal to 1 day (interquartile range: 5.25 days). The occurrence of delay was, however, not associated with the protocol (p = 0.29). Therefore, and since the number of children receiving treatment according to the latest protocol was insufficient to provide statistically significant data, both study groups were combined. Noteworthy, the overall number of delayed days was not correlated with age (rho = 0.02, p = 0.82) or associated with sex (p = 0.92).

The 5-year overall survival (OS) and event-free survival (EFS) of the analyzed group was 84.8% [95% confidence interval (CI): 78.4–91.6%] and 82.1% (95% CI: 75.3–89.5%) respectively. In the group 2002 5-year OS probability was equal to 81.3% (95% CI: 73.1–90.3%) while in group 2009 the 5-year OS was calculated as 93.2% (95% CI: 85.9–100%). Similar results were obtained for EFS. In the group 2002 5-year EFS was calculated as 78.8%

(95% CI: 70.3–88.2%) while in group 2009 it was calculated as 87.5% (95% CI: 75.4–100%). The difference in OS and EFS between protocols was not statistically significant (p = 0.13 and p = 0.15, log-rank test).

The differences in survival and hazard ratio between different risk subgroups of the study was summarized in Table II. The risk of death in patients belonging to the high-risk group was increased by 30% (HR 1.30, 95% CI: 1.08–1.57, p <0.01) when delay occurred before the 8th day of treatment and by 25% (HR 1.25, 95% CI: 1.06–1.48, p <0.01) when delay occurred before the 15th day. No statistically significant change in the risk of death was observed in patients experiencing delay before the 33rd day. The risk of death or relapse of the disease in the same group was increased by 31% (HR 1.31, 95% CI: 1.08–1.59, p <0.01) and 26% (HR 1.26, 95% CI: 1.06–1.50, p <0.01) in patients having their treatment postponed before the 8th and 15th respectively. No statistically significant change in the risk of death or relapse was observed among patients experiencing delays before the 33rd day. The results concerning patients belonging to the intermediate risk group were consistent with observations made in the high-risk group. However, analysis of the data showed that the results were statistically insignificant. The Cox proportional hazards model could not be calculated in the standard risk group since there were not enough cases of death or relapse post-induction phase among these patients, as shown in Table II.

A higher incidence of adverse initial condition was observed in the high-risk group of patients compared to the standard and intermediate risk groups combined. Disease complications were reported in 14 out of 31 patients in the high-risk group versus 15 out of 96 patients in the SR and IR groups (chi^2 test, p <0.001).

Same observations were made regarding the 5-year overall survival and event-free survival of patients in respective risk groups (Table II). Although detrimental effect of delays was observed in groups of standard and intermediate risk, the results that were obtained proved to be statistically insignificant. However, in the high-risk group, interval before the 8th day once again proved to have the most detrimental effect on the outcome of treatment, lowering the 5-year OS by 44.1% (p = 0.003) and 5-year EFS by 48.6% (p = 0.002). The influence of intermission before the 15th and before the 33rd day wasn't statistically significant in the high-risk group of patients.

An increase in white blood cell count by one thousand was associated with a slight increase in the risk of death (HR 1.002, 95% CI 1–1.004, p = 0.03) and a slight increase in the risk of death or relapse (HR 1.003, 95% CI 1.001–1.004, p = 0.004). Steroid resistance was proven to have no statistically significant influence on the risk of death (HR 3.22, 95% CI: 0.93–11.13, p = 0.06). However, its impact on the risk of death or relapse was noted to be statistically significant (HR 5.61, 95% CI: 2.05–15.39, p <0.001).

Delay in treatment was reported to be most impactful during the first 8 days of treatment, both for the 2002 and 2009 protocols (p <0.01 for both protocols, regarding both OS and EFS). After analyzing the groups of patients from both protocols as a homogenous group, it was established that the risk of death due to delay before the 8th day of treatment increases by 30% (HR 1.30, 95% CI: 1.14–1.48, p <0.001), whereas the death or relapse risk increases by 33% (HR 1.33, 95% CI: 1.16–1.53, p <0.001).

Intermissions that occurred in latter days did not have such impact on the outcome of treatment. Delay before the 15th day of treatment was statistically significant regarding the hazard ratio of patients, with the risk of death for both groups combined elevated by 14% (HR 1.14, 95% CI: 1.01–1.28, p = 0.03) and the risk of death or relapse by 13% (HR 1.13, 95% CI: 1.01–1.27, p = 0.03).

Using the Kaplan-Meier survival and log-rank test, the risk of death (OS) and the risk of relapse or death (EFS) was found to be different between patients with and without delay in the 8th day of treatment (p = 0.002, Figure 2A and p = 0.005, Figure 2B respectively). These findings did not repeat in patients experiencing intermission in treatment before the 15th day or the 33rd day of treatment, where no statistically significant difference in OS and EFS was observed.

The occurrence of delay at any point of the induction phase in the treatment protocol was associated with a higher risk of death. However, its impact was not statistically significant (HR 3.99, 95% CI: 0.92–17.36, p = 0.065). Any postponement in drug administration resulted in a statistically significant elevated risk of relapse or death (HR 4.77, 95% CI: 1.11–20.49, p = 0.036). There was a noticeable difference in the 5-year OS and EFS of patients depending on the presence of delay. Children in which delay during the induction phase was reported had a statistically significant worse 5-year overall and event-free survival (p = 0.046, Figure 2C and p = 0.02, Figure 2D respectively).

Finally, the basic characteristics, shown in Table III, analyzed in comparisons between the delayed and the non-delayed before the 8th day group and the delayed and the non-delayed at any point of the induction phase group didn't show any statistically significant differences.

Discussion

The results of this retrospective analysis suggest that the occurrence of delay in specific moments in early phases of treatment protocol may increase both the risk of death and the risk of relapse or death. This analysis was done on a representative group since all known risk factors are also applicable in children included in this study. Our results are contradictory to previous reports. In a retrospective study by Yeoh et al. [6] no difference in the risk of relapse in children with shorter or longer delays in therapy was

Table II. The effect of intervals on the 5 years overall survival and event-free survival, depending on the time of delay in reference to ALLIC BFM (Berlin–Frankfurt–Munster) protocol checkpoints

	Group size	Overall survival (5 years)	Risk of death (hazard ratio)	Number of deaths	Event-free survival (5 years)	Risk of death or relapse (hazard ratio)	Number of deaths or events
	HR: 31 children						
Interval before day 8	11	87.7% vs. 43.6% (p = 0.003)	1.30 (95% CI: 1.08–1.57, p <0.01)	6	82.7% vs. 34.1% (p = 0.002)	1.31 (95% CI: 1.08–1.59, p <0.01)	7
Interval before day 15	9	79.7% vs. 53.3% (p = 0.12)	1.25 (95% CI: 1.06–1.48, p < 0.01)	4	75.2% vs. 37.0% (p = 0.06)	1.26 (95% CI: 1.06–1.50, p < 0.01)	5
Interval before day 33	20	90.0% vs. 67.5% (p = 0.26)	1.02 (95% CI: 0.78–1.34, p = 0.88)	6	90.0% vs. 53.3% (p = 0.1)	1.04 (95% CI: 0.83–1.29, p = 0.72)	8
	IR: 68 children						
Interval before day 8	24	90.0% vs. 74.1% (p = 0.11)	1.51 (95% CI: 0.90–2.54, p = 0.12)	6	90.6% vs. 74.3% (p = 0.1)	1.51 (95%CI: 0.90–2.54, p = 0.12)	6
Interval before day 15	23	88.2% vs. 75.2% (p = 0.26)	1.11 (95% CI: 0.82–1.51, p = 0.49)	5	88.6% vs. 75.5% (p = 0.27)	1.11 (95% CI: 0.82–1.51, p = 0.49)	**5**
Interval before day 33	35	89.9% vs. 82.5% (p = 0.56)	1.10 (95% CI: 0.98–1.23, p = 0.12)	5	90.1% vs. 82.8% (p = 0.57)	1.01 (95%CI: 0.97–1.23, p = 0.12)	5
	SR: 28 children						
Interval before day 8	9	NA	NA	–	NA	NA	–
Interval before day 15	12	NA	NA	–	100% vs. 90.0% (p = 0.22)	0.98 (95% CI: 0.46–2.07, p = 0.96)	1
Interval before day 33	12	NA	NA	–	100% vs. 90.0% (p = 0.22)	0.94 (95%CI: 0.36–2.50, p = 0.91)	1

HR – high risk; CI – confidence interval; IR – intermediate risk; SR – standard risk; NA – not available

found. Moreover, a tendency for fewer relapses in patients who had a longer delay during the maintenance phase of treatment was noted [6]. Laughton et al. in another retrospective analysis reported that there is no significant association between delays at any measured time point and the risk of relapse [10]. However, the association between abandonment of therapy and the risk of death has not been investigated in any of the two mentioned studies. Koka et al. [11] in a study from 2014 investigated the influence of total delay of treatment on OS and reported that a period of interruption longer than 5 days during transition from M protocol to protocol II improved patients' OS comparing to shorter delays but no influence on EFS was noted. An association between treatment interruption and shorter OS or EFS was also rejected in a study by Wahl et al [12]. Meeske et al. [13] reported that females had significantly more

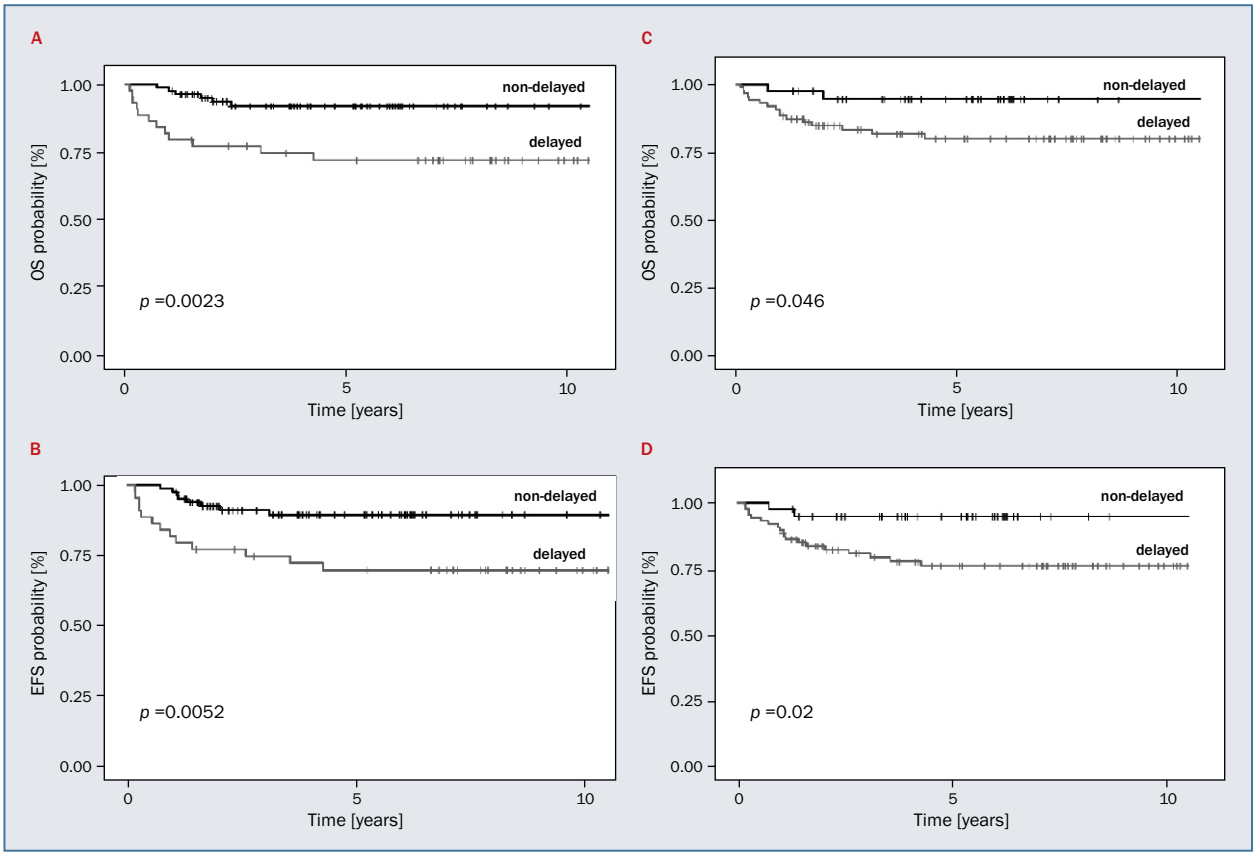

Figure 2. Graphs presenting the Kaplan-Meyer curves of overall survival (OS) and event-free survival (EFS) of patients in the whole group, depending on the occurrence of delay before the 8th day (**A, B**) and delay at any point during the induction phase (**C, D**). The presented *p* values are the result of the log-rank test

hospital days and delays in therapy than males. It should however be noted that some of the mentioned studies have major limitations. They include single center analyses with a relatively small number of patients. Considering the fact that, as mentioned above, the rates of abandonment of therapy or toxic deaths are low in high-income countries, a multiple center investigation is highly recommended for a chance of better understanding of treatment delays' influence on overall and event-free survival.

Our study demonstrates the importance of strict adherence to the protocol as even a single day of delay highly increases the risk of death and the risk of relapse or death. The first 33 days of treatment are a critical period due to the initial patient response to chemotherapy treatment, metabolic abnormalities and infections. Infections, neutropenia and febrile neutropenia can result in chemotherapy delay or changes of therapy and are commonly believed to contribute to worst outcome [14]. Prevention plays a key role in avoiding these complications. Another factor causing therapy abandonment is toxicity, which most commonly leads to early discontinuation [15].

As a retrospective observational study, our work is bound to several limitations. It should be noted that this is a single center study and a broader analysis on a bigger group of patients would be highly recommended. The sample size of patients belonging to the high-risk group is relatively small and potentially not representative enough, however, the results we obtained are alarming, as even smallest delays in this group may lead to dire consequences of higher risk of death or relapse. Furthermore, as we also have already demonstrated, initial conditions of patients also play a pivotal role in the prognosis, and it would be of great benefit to establish which of these two factors contributes more to the increased risk of death or relapse Therefore it would be wise to examine this relation further on a bigger group with a special focus on the initial patients' condition and the occurrence of delay. Another important aspect is no group division based on the protocol implemented. We decided that the differences between the two protocols are omittable for the purpose of our analysis.

The reasons for treatment interruptions in high-income countries are most commonly medical — meaning that patients with more severe disease are predestined to therapy delay because of contraindications. Postponement may be caused by complications such as infection, hypersensitivity reactions, kidney failure, thrombosis, bleeding or even

Table III. Comparison between children in which delay occurred before the 8th day of the protocol and those without such delay and between children in which delay occurred at any point of the induction phase (any-delay group) and those without any delay (no delay group) in the course of treatment

Parameter Characteristics	Delay before the 8th day Number/median	No delay before the 8th day Number /median	*P* value	Any delay Number/median	No delay Number/median	*P* value
Group size	44	83		87	40	
Median age [years]	5.88 (IQR: 2.53–2.55)	4.70 (IQR: 2.87–8.64)	0.49	5.29 (IQR: 2.53–0.64)	4.00 (IQR: 2.82–0.65)	0.99
Sex:			0.44			0.88
• girls	16	36		36	16	
• boys	28	47		51	24	
Risk group:			0.95			0.53
• SR	9	19		17	11	
• IR	24	44		47	21	
• HR	11	20		23	8	
Leukemia variant:			0.54			0.19
• T-ALL	7	10		14	3	
• BCP-ALL	37	73		73	37	
Steroid response:			0.93			0.17
• good steroid response	41	77		79	39	
• poor steroid response	3	6		8	1	
Protocol:			<0.001			0.21
• ALLIC BFM 2002	37	43		56	22	
• ALLIC BFM 2009	7	40		28	18	
Median WBC at day 1 [per μL]	17,010 (IQR: 4,900–5,000)	12,650 (IQR: 4,860–36,700)	0.70	14,175 (IQR: 5,400–46,745)	8,400 (IQR: 3,400–33,500)	0.13
OS	72.1%	92%	0.002	80.2%	94.7%	0.046
EFS	69.9%	89.4%	0.005	76.2%	94.9%	0.02
Median follow-up time	7.11 (IQR: 1.93–8.83)	4.53 (IQR: 2.09–6.27)	0.16	5.25 (IQR: 1.82–8.59)	5.28 (IQR: 3.34–6.22)	0.49

IQR — interquartile range; SR — standard risk; IR — intermediate risk; HR — high risk; ALLIC BFM (Berlin–Frankfurt–Munster); T-ALL — T-cell acute lymphoblastic leukemia; BCP-ALL — B-cell precursor acute lymphoblastic leukemia; BCP-ALL; WBC — white blood cells; OS — overall survival; EFS — event-free survival

the occurrence of weekend in the course of the calculated days of therapy protocol. Children with comorbidities, genetic diseases and those predestined to toxicity occurrence may present with lower OS and EFS which has been reported in some specific groups [16]. Distinguishing the most important factor contributing to worst survival may be troublesome in most cases. In our cohort, a difference in number of patients with delay in early phase of remission induction treatment according to treatment protocol was also noticed. This might suggest that a learning process of medical team in management of freshly diagnosed children with ALL could have an impact of delay in treatment. However, this needs to be validated on a large sample size.

Despite numerous investigations in the topic of children acute lymphoblastic leukemia, only a few analyses concerning chemotherapy delay and its association with survival have been conducted. The problem remains to be poorly understood and requires further multi center studies in order to determine its clinical importance.

Conclusion

The ALL treatment protocols have a very specific time regulation that should be strictly followed as delay in specific moments in early phases of treatment protocol may lead to worse patients' survival.

Authors' contributions

Wojciech Młynarski conceived the presented idea and supervised the project. Kaja Michalczyk, Maciej Cichosz, Maciej Zdunek gathered the necessary data, Wojciech Młynarski enabled the access to required databases and proposed the direction of investigation. Anna Puła conducted the statistical analysis (Kaplan-Meier curves, univariate Cox proportional hazards regression modelling). Anna Puła, Maciej Zdunek wrote the manuscript under supervision from Wojciech Młynarski.

Conflict of interest

The authors have no conflict of interest to declare.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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