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BRIEF REPORT

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Pulmonary embolism in acute lymphoblastic leukemia — An observational study of 1685 patients treated according to the NOPHO ALL2008 protocol

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Abstract

Background: Pulmonary embolism (PE) is a serious complication of acute lymphoblastic leukemia (ALL). We examined the cumulative incidence and clinical presentation of PE in a well-defined cohort of patients with ALL aged 1-45 years treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol.

Methods: As part of the mandatory toxicity reporting of NOPHO ALL2008, thromboembolism including PE was reported consecutively. The cumulative incidence of first-time PE was calculated using the Aalen-Johansen estimator during a 2.5-year period from ALL diagnosis. We used Fisher's exact test to examine categorical variables and Cox logistic regression to estimate hazard ratios (HRs) for PE.

Results: PE was diagnosed in 32 of 1685 patients. The 2.5-year cumulative incidence of first-time PE increased with age: 0.43% (95% CI, 0.18-1.03) in children aged 1-9 years, 3.28% (95% CI, 1.72-6.22) in children aged 10-17 years, and 7.22% (95% CI, 4.61-11.21) in adults aged 18-45 years. The majority of PEs, 78% (25/32), occurred during asparaginase treatment. HRs adjusted for age and sex were associated with male sex (HR, 2.4; 95% CI, 1.0-5.6) and older age (10-17 years: HR 7.5; 95% CI, 2.5-22.2), 18-45 years: HR, 16.5; 95% CI, 6.1-44.5). In two-thirds of the patients (63%; 17/27), PE and its treatment had no impact on the administered doses of asparaginase. PE-associated 30-day mortality was 9.4% (95% CI, 1.9-25.0).

Conclusions: Awareness of PE is warranted during ALL treatment. Larger multicenter studies are needed to examine predictors of PE in ALL.

KEYWORDS

acute lymphoblastic leukemia, asparaginase, incidence, pulmonary embolism, toxicity

Essentials

- Pulmonary embolism (PE) is a serious complication of acute lymphoblastic leukemia (ALL).
- We observed PE in 32 of 1685 patients aged 1-45 years with ALL.
- Cumulative incidence of PE was 1.9%, and being 7.2% at age 18-45years.
- Mortality of PE was 9.4%, and all fatalities (n = 3) occurred in children.

1 | INTRODUCTION

Current treatment approaches have improved the event-free survival rates for children and adults with acute lymphoblastic leukemia (ALL) to more than 80% and 74%, respectively.[1,2] Treatment of ALL is associated with toxicity, such as thromboembolism (TE), including pulmonary embolism (PE).[3-5] TE, and especially PE, is a potentially life-threatening event and may impact scheduled treatment for leukemia.[6,7] Risk factors for PE have not been validated in children, and data in the setting of PE in childhood and adulthood ALL are lacking.[8] We examined the cumulative incidence and clinical presentation of PE in a well-defined cohort of patients with ALL aged 1-45 years treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol. The study is, to our knowledge, the largest observational study ever published on PE in children and young adults with ALL.

2 | METHODS AND MATERIALS

We included children and adults with ALL aged 1-45 years treated according to the NOPHO ALL2008 protocol.[2] The NOPHO ALL2008 protocol includes Denmark, Estonia, Finland, Iceland, Lithuania, Norway, and Sweden. The patients (n = 1812) were diagnosed with ALL from July 2008 to February 2016. Patients who developed PE during treatment for ALL were identified and compared with patients without TE during ALL therapy. The following exclusion criteria were used in this study: TE other than PE (n = 122), missing data (n = 4), and ALL treatment deviating from the protocol (n = 1). The patients with TE, who were excluded from the present study, have been described previously.[7,9] Eventually, the total study cohort comprised 1685 patients. The date for the last follow-up was April 1, 2017.

Patient demographics, ALL characteristics, and treatment details were retrieved from the NOPHO ALL2008 registry. TE events were registered at 3-month intervals through mandatory toxicity registration in the NOPHO register, with a compliance rate of 98.9%.[10] In-depth information of the PEs was obtained from the hospitals retrospectively, using a standardized data registration form. Cases of symptomatic PE were identified through clinical symptoms and confirmed by imaging (computed tomography [CT] or lung scintigraphy). Asymptomatic PE was defined as an incidental finding when imaging was performed due to other symptoms without suspicion of PE or as workup due to deep venous thrombosis (DVT) elsewhere without associated pulmonary symptoms. The date of PE was defined as the date of confirmation of PE by imaging or the death date in cases of PE diagnosed by autopsy. The patients included in this study were not screened for PE. Children were defined by age below 18 years. Major bleeding was defined by the criteria of the ISTH.[11] Data on bleeding episodes for each patient were collected the following 3 months after the start of anticoagulation.

2.1 | The NOPHO ALL2008 protocol

The NOPHO ALL2008 protocol has been previously described in detail elsewhere.[2] During the first 21 days of the induction phase, patients received dexamethasone or prednisolone. The first intramuscular pegylated asparaginase (PegASP) administration (1000 IU/m^2) was scheduled on day 30. Patients were stratified into a non–high-risk (standard or intermediate), or high-risk group. From treatment week 14, children in the non–high-risk group were randomized to continue PegASP every second week (control group) or every sixth week (experimental group).[12] The high-risk group received PegASP at the end of each chemotherapy block course (approximately every third to fourth week). The NOPHO ALL2008 protocol has no specific recommendation for thromboprophylaxis, while recommendations for therapeutic anticoagulation are available at the NOPHO website.[13]

2.2 | Statistics

The study population was followed from the diagnosis of ALL until one of the following events: the date of the first event (relapse, death, or second malignant neoplasm [SMN]); stem cell transplantation in first complete remission; lost to follow-up; last follow-up in the NOPHO ALL2008 registry; or April 1, 2017. Clinical characteristics were compared between patients with and without PE using Fisher's exact test. The cumulative incidence of first-time PE was calculated using the Aalen-Johansen estimator, considering death, relapse, and SMN as competing events during a 2.5-year period from ALL diagnosis. We used crude and adjusted Cox proportional hazards analysis to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) with first-time PE as the outcome. The body mass index (BMI) in children was calculated using references by Juliusson et al.[14]

2.3 | Ethics

The NOPHO ALL2008 study was approved by the National Medicines Agencies and the relevant national or regional committees for research ethics in each participating country (Clinical Trial Registration: EudraCT 2008-003235-20 and 2011-000908-18).

3 | RESULTS

In total, 32 of 1685 patients developed PE. In 63% (n = 20) concomitant DVT was not observed. One patient had a cerebral sinovenous thrombosis, DVT, and PE at the same time. The diagnosis of PE was confirmed by CT (n = 29), lung scintigraphy (n = 1), and autopsy (n = 2). All DVTs were confirmed by ultrasonography. In 3 patients, diagnosis of PE was incidental.

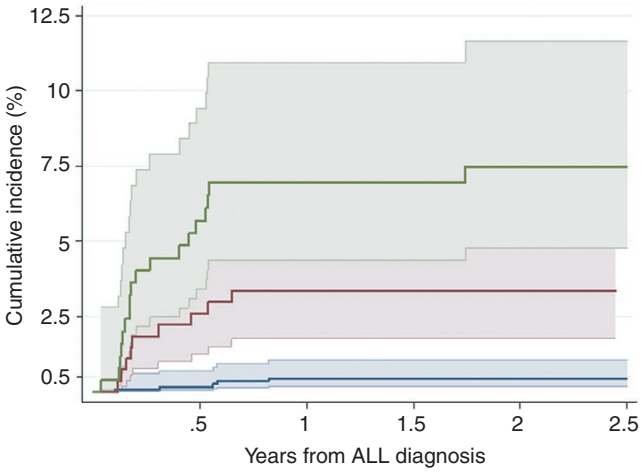

FIGURE 1 2.5-year cumulative incidence of PE is 0.43% (95% CI, 0.18-1.03), 3.28% (95% CI, 1.72-6.22), and 7.22% (95% CI, 4.61-11.21) in patients aged 1-9 y, 10-17 y, and 18-45 y, respectively. ALL, acute lymphoblastic leukemia; CI, confidence interval; PE, pulmonary embolism

The 2.5-year cumulative incidence of first-time PE during therapy was 1.91% (95% CI, 1.35-2.69). Increasing age was associated with a higher risk of PE (Figure 1). Children aged 1-9 years and 10-17 years experienced PE corresponding to a 2.5-year cumulative incidence of 0.43% (95% CI, 0.18-1.03) and 3.28% (95% CI, 1.72-6.22), respectively. PE occurred with the highest incidence of 7.22% (95% CI, 4.61-11.21) among adults (18-45 years).

Eighteen patients (56%; 18/32) had infection at the diagnosis of PE. Of those, 8 patients (44%; 8/18) had positive blood cultures. Immobilization ≥3 days was reported in 5 cases at time of PE. Smoking (n = 2) and oral contraceptive use (n = 2) were additional risk factors in adults (n = 18). D-dimer at the time of PE diagnosis was elevated (cutoff >0.5 mg/L) in all but 1 of 23 cases with available D-dimer analyses.

The majority of PE cases in the non–high-risk ALL treatment group occurred during consolidation I (protocol weeks 5-13) and during maintenance I (protocol weeks 20-57) (Figure 2). In these phases of treatment, patients were under concomitant PegASP and steroid treatment. Five of 6 patients who received high-risk chemotherapy developed their PE after the first chemotherapy block A. (Figure 2). In 78% (25/32) of PE cases, PE occurred within 4 weeks from the last PegASP administration. Two thirds of the patients with available data

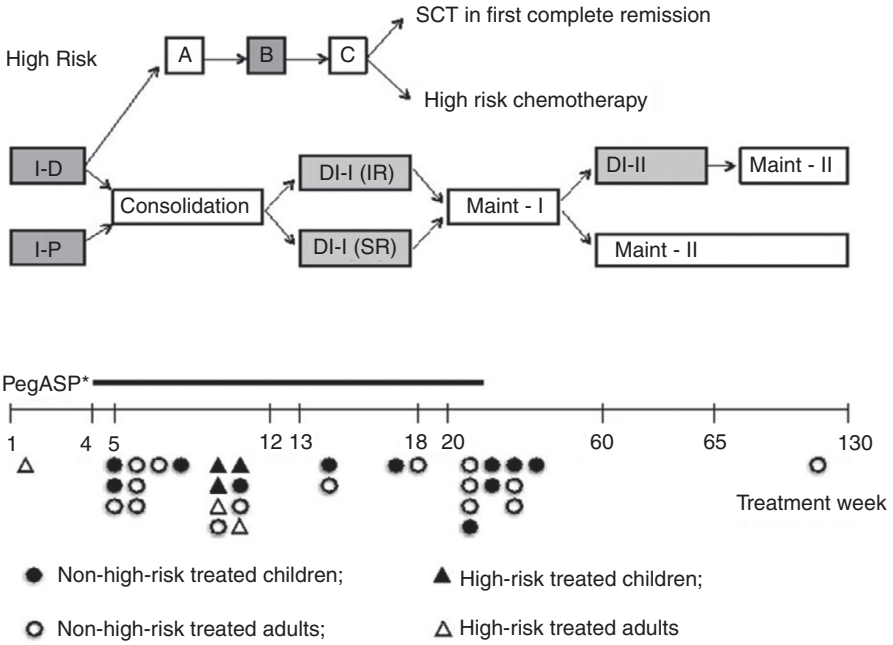

FIGURE 2 Time point for diagnosis of pulmonary embolism (n = 32) in relationship with an overview of the treatment phases of the NOPHO ALL2008 protocol. Treatment weeks at the bottom of the figure apply to non–high-risk treatment. *The treatment with PegASP in the non–high-risk group started postinduction on day 30 and continued until treatment week 33 (as shown at the bottom of the figure with the horizontal line). The patients in the high-risk group received PegASP at the end of each high-risk block. Treatment phases with steroids are indicated in gray. The triangles and the dots are explained at the bottom of the figure. Children are defined as 1-17 y old; adults 18-45 y old. DI-I, first delayed intensification; DI-II, second delayed intensification; I-D, induction therapy with dexamethasone; I-P, induction therapy with prednisolone; IR, intermediate risk protocol; Maint-I, first maintenance; Maint-II, second maintenance; PE, pulmonary embolism; PegASP, pegylated asparaginase; SCT, stem cell transplantation

TABLE 1 Clinical characteristics, univariate Cox regression, and Cox regression adjusted for age and sex in ALL patients (1-45 y) with PE (n = 32) and without PE (n = 1653)

Factor	PE n = 32 (%)	No PE n = 1653 (%)	*P* value	HR (95% CI)	
				Univariate Cox regression	Cox regression adjusted for age and sex
Age, y[a]					
1-9	5 (15.6)	1155 (69.9)	<.001	Ref.	Ref.
10-17	9 (28.1)	265 (16.0)		7.8 (2.6-23.3)	7.5 (2.5-22.2)
18-45	18 (56.3)	233 (14.1)		17.7 (6.6-47.6)	16.5 (6.1-44.5)
Sex					
Female	7 (21.9)	747 (45.2)	.01	Ref.	Ref.
Male	25 (78.1)	906 (54.8)		2.9 (1.2-6.7)	2.4 (1.0-5.6)
ALL phenotype					
B-precursor	20 (62.5)	1393 (84.3)	.003	Ref.	Ref.
T-cell/bilineage	12 (37.5)	260 (15.7)		3.2 (1.6-6.6)	1.6 (0.8-3.3)
Induction[b]					
Prednisolone	19 (59.4)	1285 (78.5)	.05	Ref.	Ref.
Dexamethasone	13 (40.6)	352 (21.5)		2.5 (1.3-5.1)	1.3 (0.6-2.7)
WBC at ALL diagnosis[‡]					
<100 × 10^9/L	26 (81.3)	1429 (86.5)	.43	Ref.	Ref.
≥100 × 10^9/L	6 (18.8)	223 (13.5)		1.5 (0.6-3.7)	1.2 (0.5-2.8)
ALL therapy after day 29[§]					
Non–high-risk	26 (81.3)	1343 (82.3)	.82	Ref.	Ref.
High-risk	6 (18.8)	288 (17.7)		1.1 (0.5-2.7)	0.5 (0.2-1.3)
Residual disease after day 29 [¶]					
<5%	30 (93.8)	1503 (92.7)	1.0	Ref.	Ref.
≥5%	2 (6.3)	118 (7.3)		0.9 (0.2-3.7)	0.4 (0.1-1.6)
Mediastinal masses[**]					
No	25 (78.1)	1516 (92.9)	.007	Ref.	Ref.
Yes	7 (21.9)	116 (7.1)		3.6 (1.6-8.4)	1.9 (0.8-4.5)
Enlarged lymph nodes ≥ 3cm[††]					
No	26 (86.7)	1510 (93.0)	.16	Ref.	Ref.
Yes	4 (13.3)	114 (7.0)		2.1 (0.7-6.0)	1.4 (0.5-4.0)
BMI[††]					
Normal weight	20 (62.5)	1400 (85.4)	<.001	Ref.	Ref.
Underweight (<−2SD)	0 (0)	110 (6.7)		0	0
Overweight (> +2SD)	12 (37.5)	129 (7.9)		6.4 (3.1-13.1)	2.2 (0.9-4.9)

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; CI, confidence interval; HR, hazard ratio; PE, pulmonary embolism; Ref., reference; SD, standard deviation; WBC, white blood cell count.

[a]Age at ALL diagnosis.

[b]Two patients without PE are not included—1 patient received no steroid treatment in induction due to viral infection, and another patient had modified induction. Data are not available in an additional 14 patients without PE.Data not available in following number of patients without PE:

[‡]n = 1,

[§]n = 22,

[¶]n = 32,

[**]n = 21,

[††]n = 29,

[§§]n = 14.

(63%; 15/24) received steroids at the time or within 14 days before PE diagnosis. Demographic characteristics of patients with and without PE are shown in Table 1. Patients with PE were older with a higher proportion of male sex, had a higher BMI, a higher proportion of T-cell ALL and mediastinal mass compared with patients without PE.

In univariate regression analyses, increasing age, male sex, overweight, T-cell ALL, induction with dexamethasone, and the presence of lymphadenopathy and mediastinal mass were associated with PE development (Table 1). No other predictors to PE than male sex (HR, 2.4; 95% CI, 1.0-5.6) and older age (10-17 years: HR, 7.5; 95% CI, 2.5-22.2), 18-45 years: HR, 16.5; 95% CI 6.1-44.5) were identified in analyses adjusted for sex and age (Table 1).

Three children with PE died (n = 3/32) corresponding to PE-associated 30-day mortality of 9.4% (95% CI, 1.9-25.0). PE directly caused the death of a 1-year-old boy with respiratory compromise and cardiac arrest. PE was a contributing factor to death caused by septicemia in 2 children: a 4-year-old boy was diagnosed with PE by autopsy, and a 5-year-old girl had PE confirmed by CT while on extracorporeal membrane oxygenation support. In our study, patients with PE (n = 29) were treated with low-molecular-weight heparin (LMWH) (n = 27) or unfractionated heparin (n = 2). Non–K-vitamin antagonists after initial LMWH treatment were administered in 2 adults and in one 17-year-old patient.

Two minor bleedings (epistaxis) and a major bleeding were registered during the therapeutic anticoagulation period. A 13-year-old boy experienced hemothorax during catheter-directed thrombolysis. This child fully recovered. No fatal bleedings occurred. None of the patients diagnosed with PE at the pediatric departments had received primary antithrombotic prophylaxis, while 4 patients treated at the adult clinics were on LMWH prophylaxis before the diagnosis of PE. In two thirds of our patients (63%; 17/27), PE and/or its treatment had no impact on the administered total dose of PegASP.

4 | DISCUSSION

Our study is the first we are aware of to report the cumulative incidence of PE in ALL patients treated according to a uniform protocol. In pediatric populations, the incidence of PE peaks in infancy (age <1 year) and adolescence.[15] In our cohort, which does not include infants <1 year of age, the highest 2.5-year cumulative incidence was not in children but in adults aged 18-45 years, which is not a surprise since PE is more common in adults.[16]

In this study, most PEs occurred during concomitant treatment with asparaginase and steroids. Asparaginase decreases anticoagulant, procoagulant, and fibrinolytic protein levels, especially reduction in antithrombin results in hypercoagulability and increased risk of thrombosis.[17] Exposure to asparaginase, increasing age, T-cell leukemia, mediastinal mass, obesity, and use of dexamethasone in induction have previously been pointed out as possible factors for increased risk of TE in ALL.[18-22] In our study, older age was associated with a higher risk of PE. We also observed a greater proportion of male sex in patients with PE. Male predominance in PE has not been previously reported in children or young adults without malignancies.[16,23] To date, no other studies have focused on PE in pediatric and young adult ALL; thus, our finding needs to be confirmed and should be interpreted with caution due to few observations and limited statistical power in our study. In a study by Prasca et al,[22] obesity was a significant risk factor to DVT in children with ALL. A tendency toward an association between increased BMI and PE was observed, although not statistically significant. However, overweight can be an amenable factor, and therefore this observation should be investigated in larger studies, too. In our cohort, PEs occurred after induction and continued during the first 6 months of ALL treatment, which coincides with PegASP treatment. Reexposure to asparaginase with LMWH cover has previously been reported to be safe once symptoms of TE have resolved.[24] In our patients, treatment with LMWH was without major complications, and in most cases, asparaginase was not truncated.

In conclusion, PE is a potentially fatal complication during the treatment of ALL. Our population-based study emphasizes the need for awareness of PE during the exposure of asparaginase and steroids.

RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of the article and met the required conditions for authorship. RT, OGJ, SL, CUR, SR, KS, SST, and ER designed the study and collected, analyzed, and interpreted the data. CLB conducted statistical analyses and interpreted the data. RT and CBL wrote the article. All the authors revised the article for critical content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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