



Obesity is Not Associated with An Increased Risk of Venous Thromboembolism in AYA Patients with Acute Lymphoblastic Leukemia

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Abstract

Context: Acute venous thromboembolisms (VTE) are a serious complication during intensive chemotherapy. Risk factors associated with VTEs, specifically in the adolescent and young adult (AYA) population being treated per pediatric protocols for acute lymphoblastic leukemia (ALL) are poorly described in the literature. **Objective:** To determine whether baseline demographic data, specifically obesity and asparaginase dose, are risk factors for VTE in AYA patients. **Design, Setting, and Patients:** Patients were studied retrospectively from 2009—2020. Tertiary referral center. A cohort of 66 adolescent and young adult patients, ages 15 to 26 years, with previously untreated ALL were identified and divided into groups based on presence or absence (controls) of VTE during ALL treatment. All patients were treated with Berlin-Frankfurt-Münster (BFM)-based pediatric chemotherapy protocols. **Main Outcome Measures:** We hypothesized that AYA patients being treated per BFM-based pediatric protocols experience similar or higher rates of VTE to the pediatric ALL population, and that the risk of developing a VTE is increased in patients as body mass index (BMI) and asparaginase dose increases. **Results:** Fourteen patients (21%) experienced 17 VTEs. The majority of VTEs occurred during induction chemotherapy (47%), after asparaginase administration (88%), in the upper extremities (59%), were associated with a CVC (53%), and were treated with anticoagulation (94%). BMI or asparaginase dose during induction chemotherapy were not predictive of VTE risk (p=0.9). There were no statistical differences in age at diagnosis, sex distribution, race/ethnicity distribution, other treatment-related morbidities, relapse free survival (79% vs. 81% at 5 years), and overall survival (93% vs. 81% at 5 years) in patients who experienced a VTE compared to controls, respectively. **Conclusions:** AYA patients with ALL experienced similar rates of VTE to their pediatric counterparts. Unlike adults with cancer, increased BMI and asparaginase dose were not associated with an elevated risk of VTE. Given the limited study size and retrospective nature of this study, future prospective studies are indicated before this information is appropriate for clinical application.

Background

Venous thromboembolism (VTE) is associated with increased morbidity, mortality, and higher healthcare costs in adult and pediatric patients with cancer. BFM (Berlin-Frankfurt-Münster)-based ALL (acute lymphoblastic leukemia) chemotherapy protocols utilize high-dose steroids and PEG-asparaginase usually administered through a central venous catheter (CVC), all of which are associated with an increased risk of thrombosis. However, the incidence and risk factors of VTE are not well described in AYA (adolescent and young adult) leukemia patients with ALL treated per pediatric protocols. Identifying risk factors predictive of developing VTEs in this population is important for introducing prompt and timely prophylactic measures aimed at reducing healthcare costs and morbidity. In childhood ALL the incidence of VTE is low. In AYA patients with cancer, the cumulative incidence of VTE has been reported as high as 41%. Known factors increasing the risk of developing a VTE in children with ALL include older age, obesity, T-cell phenotype, L-asparaginase chemotherapy, prednisone use, personal and family history of thrombotic events, and CVC use. In adults with cancer, obesity and elevated baseline platelets have been associated with increased thrombotic events. In adults with ALL, VTE risk is increased using pediatric-inspired regimens that utilize high-dose steroids and PEG-asparaginase. We hypothesized that AYA patients being treated per BFM-based pediatric protocols experience similar or higher rates of VTE to the pediatric ALL population, and that the risk of developing a VTE is increased in patients as body mass index (BMI) increases.

Objective

The mean age of the cohort was 18±3 years, and most were male (62%), white (92%) and a healthy weight at diagnosis (48%). There were 17 VTEs identified in 14 patients. The median time to first VTE was 27 days (range 4—242 days). The majority of VTEs were deep venous thrombosis in the upper extremity (n=10, 59%), were treated with anticoagulation (n=16, 94%), and were CVC-associated (n=9, 53%). No patients who developed a VTE had prophylactic anticoagulation, and none had a personal history of thrombosis. Three patients had repeat VTEs. BMI was similar in the VTE cohort and controls (27.0±7.3 vs. 26.7±7.1 kg/m², p=0.9). There was no increased risk for VTE associated with increasing BMI (OR=1.00, CI=0.97—1.04). Relapse-free survival (79% vs 81% at 5 years, p=0.4) and overall survival (93% vs 81% at 5 years, p=0.6) were similar in the patients who developed a VTE compared to controls (Figure 1).

	Total* 18±3	VTE Group* 19±3	Control Group* 18±3	P-value
Age (years)				0.1
Sex				0.8
-Female	25 (38%)	6 (43%)	19 (37%)	
-Male	41 (62%)	8 (57%)	33 (63%)	
Race				0.3
-Black	5 (8%)	2 (14%)	3 (6%)	
-White	61 (92%)	12 (86%)	49 (94%)	
Ethnicity				0.3
-Latinx	6 (9%)	0	6 (12%)	
-Not Latinx	60 (91%)	14 (100%)	46 (88%)	
Dose of asparaginase (IU)	4832±771	4800±793	4841±773	0.9
Average BMI (kg/m²)	26.8±7.1	27.0±7.3	26.7±7.1	0.9
-Odds Ratio (95%CI)			1.00 (0.97, 1.04)	0.9
BMI Categories				0.3
-Underweight	3 (5%)	1 (7%)	2 (4%)	
-Healthy weight	32 (48%)	5 (36%)	27 (52%)	
-Overweight	13 (20%)	5 (36%)	8 (15%)	
-Obese	18 (27%)	3 (21%)	15 (29%)	
Class 1	10 (15%)	1 (7%)	9 (17%)	
Class 2	5 (8%)	1 (7%)	4 (8%)	
Class 3	3 (5%)	1 (7%)	2 (4%)	
Treatment Morbidities and Mortality				
-Asparaginase allergy	21 (32%)	4 (29%)	17 (33%)	1.0
-Refractory disease	8 (12%)	0	8 (15%)	0.2
-Relapse	10 (15%)	3 (21%)	7 (14%)	0.4
-Death	8 (12%)	1 (7%)	7 (14%)	1.0
* n (%), mean±standard deviation				
BMI = body mass index; CI = confidence interval; IU= international unit; VTE = venous thromboembolism.				

Materials & Methods

We identified a cohort of 66 AYA patients (age range 15—26 years) treated at Riley Hospital for Children, Indiana University from 2009-2020 for high-risk B and T-ALL and conducted a retrospective chart review. Patients were placed into two groups based on whether they had a VTE or not (controls). Fisher’s Exact or t-tests were used for categorical and continuous variables, respectively. Logistic regression, with hazard ratio and 95% confidence intervals (CI), was used to analyze potential risk factors for VTE. Analyses were performed in SAS version 9.4. Adult BMI categories per Center for Disease Control and Prevention (CDC) were utilized to define obesity as BMI of 30.0 or higher, overweight as BMI of 25.0—29.9, healthy weight as 18.5—24.9, and underweight as BMI <18.5 kg/m². Similarly, CDC categories were used to define class 1 obesity as 30.0—34.9, class 2 obesity as 35.0—39.9, and class 3 obesity as >40.0 kg/m².

Summary

1. Our patients experience similar rates of VTE compared to their pediatric counterparts.
2. Those who had a VTE did not have prophylactic anticoagulation.
3. Higher BMI was not associated with higher rates of VTE in our AYA cohort, in contrast to their pediatric and adult counterparts.
4. Large prospective studies are needed to elicit the role of anticoagulation prophylaxis in these patients.

Discussion

One in five patients developed a VTE, and similar to previously published pediatric studies, the majority of VTE’s occurred after receiving asparaginase. Obese adult and pediatric cancer patients are at higher risk of developing a VTE. However, in our AYA patient cohort, the number of VTEs in obese patients was similar to patients who were underweight, normal weight, and overweight. This finding is corroborated by other VTE studies in AYA oncology patients. The findings of our study should be interpreted with caution as it is limited by its retrospective nature and small sample size. Our cohort had few obese patients, and it is plausible that other unidentified risk factors including adverse cytogenetics, genetic predisposition, and prolonged immobilization may have influenced or biased the findings of our study. Nevertheless, this study highlights the need for larger prospective studies to proactively identify AYA patients with ALL at a higher risk of developing a VTE and help establish standardized practices for anticoagulation prophylaxis for this common complication.

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