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Safety and feasibility of lower antithrombin replacement targets in adult patients with hematological malignancies receiving asparaginase therapy

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Summary

The optimal antithrombin(AT) activity parameters for replacement as thromboprophylaxis following asparaginase remains unclear. This single-center, retrospective study evaluated two sets of AT replacement thresholds and targets in adults receiving asparaginase-containing chemotherapy. AT supplementation adhered to institutional standards, which lowered the AT activity target from 100% to 80% in 6/2014. Ninety-two patients were evaluated. Cumulative thrombosis incidence was 16% at 6 months (95%CI:6.8–24.0, maximum follow-up 315 days) with similar incidence between the 80% and 100% target groups, 14% (2 of 14) and 13% (10 of 78), respectively, with a small non-Line-Related DVT incidence (3%). Most thrombotic events occurred during induction chemotherapy and demonstrated no associations with replacement target, cumulative days or cumulative area under AT activity target, number of asparaginase doses, or cumulative asparaginase dose. Median estimated AT replacement expenditure was \$34,963USD

(IQR \$16,260USD to \$79,319USD) per patient. Cost-effectiveness and optimization of AT replacement for thromboprophylaxis following asparaginase requires prospective evaluation.

Keywords

Antithrombin; Asparaginase; Thrombosis; Thromboprophylaxis; Hematological Malignancy

Introduction

Thrombotic complications following asparaginase chemotherapy are a well-recognized cause of morbidity in patients with malignancy.[1] Systemic depletion of asparagine prevents the synthesis of proteins and leads to a decrease in antithrombin (AT) and fibrinogen.[2,3] Complication rates of thrombosis following asparaginase administration range between 4.2% and 34%.[4–7] Improved purification processes and a newer pegylated formulation have renewed interest in asparaginase therapy; however, concerns still exist regarding the overall impact and management of asparaginase related-coagulopathies.[8]

The only prospective analysis of AT supplementation occurred in pediatric patients receiving L-asparaginase (LASP) and showed a trend towards reduced incidence of thrombosis in patients receiving AT compared to the control arm (28% vs. 37%).[9] Retrospective analyses have demonstrated a statistically significant reduction in thromboembolic complications when utilizing AT replacement compared to no replacement; however, these studies contain small sample sizes and lack cost considerations.[4,10] Current guidelines do not comment on AT replacement as a supportive management strategy for asparaginase toxicity.[11] The existing consensus recommendation for institutions that desire to administer thromboprophylaxis following asparaginase include AT replacement alone or in combination with low-molecular-weight heparin when the AT activity level is 60% or less, without definitive recommendations for AT activity targets or coagulation factor monitoring.[8]

The paucity of data regarding AT repletion in adults, particularly with the advent of pegylated asparaginase (PEGASP), requires further investigation. Based on expert recommendations and institutional experience, our practice is to provide AT repletion when monitored AT activity levels decline after asparaginase administration.[4, 8] The purpose of this study was to evaluate adult cancer patients with LASP- or PEGASP-induced AT deficiency, for thromboembolic outcomes during intensive AT replacement.

Methods

This single center, retrospective chart review was approved by the Institutional Review Board and conducted at Mayo Clinic Hospital, Rochester, Minnesota. Consecutive adult cancer patients receiving any asparaginase product between January 2000 and June 2016 were evaluated. Patients were excluded if they did not receive AT replacement after asparaginase, had incomplete records, had a documented hereditary thrombophilia, had a history of a pre-existing thromboembolic or hemorrhagic event, were considered a vulnerable population, or refused consent for research participation.

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Patient records were evaluated for up to 60 days after the last dose of the prescribed asparaginase formulation. Baseline information was abstracted after malignancy diagnosis but prior to chemotherapy administration. Radiologic data including computed tomography, ultrasound, or magnetic resonance imaging were reviewed for objectively confirmed thrombus or hemorrhage. Symptomatic and incidental events were recorded. AT supplementation occurs as part of our institutional standard, described as follows: Serial AT measurements are obtained after asparaginase administration at a frequency determined by the provider discretion based on clinical judgment and evaluated until a lack of coagulation factor depletion is demonstrated. Antithrombin repletion with an intended goal of achieving physiological AT activity levels (AT normal value range: 80%–120%) with a dose based on the pre-therapy plasma AT activity level, utilizing the weight-based, goal-directed formula recommended by the manufacturer in the prescribing information of the antithrombin III, human (Thrombate III®) package insert: units required (IU) = [(desired AT activity level - current AT activity level) × weight in kg] / 1.4.[12] Prior to June 2014, the strategy for AT replacement was supplementation at an AT activity level less than 70% to a target of 100%. After June 2014, the replacement threshold and target was modified to provide supplementation for an AT activity level less than 60% to a target goal of 80%. AT concentrate cost was estimated by standardizing expense to the Centers for Medicare & Medicaid (CMS) single drug historical pricing guide for therapy administered between 2000 and 2004. AT concentrate cost beginning January 1, 2005 was derived from the CMS average sales price (ASP) reported quarterly. To adjust for trends in regimen utilization that could create inaccurately weighted AT expenditure due to inflation, a subsequent adjustment was also made to calculate AT expense based solely on pricing at the close of 2016. The primary outcome was the incidence of thromboembolic complications. Secondary outcomes included a comparison of AT repletion practices, treatment- and replacement-specific factors for an association with thrombosis, and a description of estimated AT supplementation expenditures.

Baseline patient characteristics are summarized with counts and percentages for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. Comparisons of these characteristics were made between the two target groups using a T-test or Wilcoxon rank sum test as appropriate for continuous variables, and a chi-square test or Fisher's exact test for categorical variables. Survival analysis looking for the time to thromboembolic complications after asparaginase initiation was performed using the Kaplan-Meier method and Cox proportional hazards regression. Multivariable Cox proportional hazards regression was performed to assess the association between AT target group and thrombosis risk after controlling for factors known to influence thrombosis. The cumulative number of asparaginase doses given, the cumulative total dose received, the cumulative days under target, and the cumulative area under the AT activity level by time curve were treated as time dependent covariates. The cumulative area under AT activity level by time the curve measures how far under target a patient is over a period of time (in AT activity level units per month). Statistical significance was set at a p value 0.05. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2014).

Results

Ninety-two (88%) of the 104 patients screened met criteria for study inclusion and were evaluated over 8,499 total days of follow up. Refusal of research authorization (n=2), incomplete records precluding inclusion (n=4), non-utilization of AT replacement during asparaginase treatment (n=3) or being categorized as a vulnerable population (prisoners, n=3) were reasons for exclusion. There were 78 patients receiving AT supplementation to reach a target AT activity level of 100% and 14 patients who received AT replacement using the modified protocol reducing the AT activity level target to 80%. Baseline demographics and clinical characteristics are represented in table I. The median age was 41 years (IQR 26–57), 55% were male and 86% were Caucasian. The predominant diagnosis was ALL (86%) with 53 patients (57%) diagnosed with B-cell ALL (Philadelphia chromosome (Ph) positive (n=15) and Ph negative (n=38)) and 27 (29%) having T-cell ALL. Fifty-three (58%) patients received treatment for a new diagnosis and 39 (42%) were treated for relapsed disease (first relapse (n=28) and second relapse (n=11)). Median baseline AT activity and fibrinogen levels (Normal value range: 200–430 mg/dL) were 99% (IQR 89% to 110%) and 357 mg/dL (IQR 282 mg/dL to 483 mg/dL), respectively. With the exception of a higher median baseline hemoglobin in the AT group targeting an AT activity level of 80% (12.3 vs 10.1, $p=0.0092$), there were no other statistically significant differences with regards to baseline demographics and disease-related characteristics.

Eight different combination chemotherapy regimens were employed. The combination chemotherapy protocol distribution and corresponding dose schedule per asparaginase product is outlined in table II. Thirty-five (38%) patients received LASP, 52 (56%) received PEGASP and 5 (6%) received both formulations. Three patients transitioned to PEGASP due to adverse reactions experienced with LASP and two patients requested PEGASP treatment because of the reduced dosing frequency. A total of 2007 AT activity levels were analyzed (median of 14, IQR: 6–27 measurements per patient) resulting in 465 doses of AT replacement. Infusions of antithrombin III were well tolerated and without any significant adverse events. The median time to first antithrombin activity measurement after asparaginase was 2 days (IQR 1–4 days). AT activity measurements were repeated at frequencies determined by the provider, but generally occurred within 2–3 days of the antithrombin concentrate administration. When stratified by formulation, there was a median 16 (IQR: 8–30) AT activity measurements per patient for those receiving PEGASP, compared to a median 9 (IQR: 3–22) measurements for patients receiving LASP.

Cumulative incidence of thrombosis was 16% at 6 months (95% CI 6.8–24.0, with a maximum follow-up of 315 days) and is shown stratified by target level group in figure 1. All events were symptomatic and most (93%) occurred during induction chemotherapy. There was no association between the target AT activity level and the risk of thrombosis (HR 0.995 for 80% target group vs. 100% target group, 95%CI: 0.22–4.45, $p=0.9948$). Additionally, there was no significant association between cumulative number of asparaginase doses (HR 1.10, 95%CI: 0.96–1.27 per dose, $p=0.18$) or cumulative total dose of asparaginase (HR 1.04, 95%CI: 0.94–1.14, $p=0.48$). Lastly, there was no significant association between the cumulative days that AT activity level was under the target replacement threshold per week (HR 1.024, 95%CI: 0.79–1.34, $p=0.86$) or the cumulative

area under the AT activity level by time curve (HR 1.002 per AT activity % per month, 95%CI: 0.93–1.09, $p=0.95$). Multivariate analysis was unrevealing for age, sex, BMI, cancer diagnosis, immunophenotype, smoker status, regimen, asparaginase formulation, concomitant steroid type, catheter type and catheter location with resultant hazard ratios between 0.96 and 2.53 and p -values ranging between 0.20 and 0.999.

Patient specific details are shown in table III. The median AT activity level at time of TE was 58.5% (IQR 50–67). All events were symptomatic and confirmed with radiologic imaging. Additionally, none of the patients diagnosed with a TE had an active infection at the time of event occurrence. A majority (80% at 6 months) of the events were line-related deep venous thrombosis (LRDVT) treated with various conventional strategies including line removal ($n=6$), anticoagulation ($n=2$), line removal and anticoagulation ($n=3$) and warm compresses (+/- elevation) without intervention ($n=1$). Two patients had recurrent LRDVT in different locations during subsequent chemotherapy in spite of ongoing AT supplementation. The single case of pulmonary embolism (PE) was managed with systemic anticoagulation. The patient diagnosed with cavernous venous sinus thrombosis was initiated on comfort measures in the setting of multiorgan failure secondary to leukemia related complications. There were 3 hemorrhagic events in the 92 evaluated patients. All events occurred in the 100% AT activity target arm.

The reimbursement price of AT concentrate in 2000 was estimated at 1.50 USD/unit and increased to 3.68 USD/unit in the second quarter of 2016 at the time of completion of follow up. The median cost of AT replacement was 19,291 USD per patient. Adjustment to 2016 pricing amongst all regimens increased the median cost to 34,963 USD per patient. Protocol CALGB 10403 was associated with the utilization of, the highest median number of AT doses per patient ($n=18$). The intensity of PEGASP administration coupled with more extensive AT supplementation contributed to a significantly higher median expense for AT replacement, amounting to 118,064 USD per patient as depicted in figure 2. Protocol CALGB 10403 was the only regimen to omit dose capping at the time of evaluation leading to overall higher doses per body surface area.

Discussion

This study summarizes the incidence and describes the thromboembolic complications in adult patients with malignancy receiving AT as thromboprophylaxis during LASP or PEGASP containing chemotherapy regimens. We demonstrate an overall thrombosis rate of 16% at 6 months after initial asparaginase administration, with most events occurring during the induction phase of chemotherapy. LRDVT was the most common thrombotic event ($n=12$), with a low incidence of non-LRDVT (one PE, one superficial thrombophlebitis, and one cavernous venous sinus thrombosis). Antithrombin activity monitoring and subsequent AT replacement occurred at physician discretion, but was in accordance with our institutional standard. Many different treatment- and AT replacement-specific factors demonstrated no association with the development of thrombosis during our evaluation. Cost of AT replacement varied by type of asparaginase formulation administered and dose intensity, with patients on protocol CALGB 10403 incurring the greatest expense.

Alterations in hemostatic and anticoagulant pathways are a well-known complication of asparaginase with a variable reported incidence of thrombosis in adult patients.[2–5,10] Differences in thrombosis rates across studies reflect variations in study design, inclusion of asymptomatic screening, the use of prophylactic anticoagulants, and inconsistent definitions for thrombotic events. Grace, et al performed a retrospective analysis of adults with newly diagnosed ALL receiving combination-chemotherapy including asparaginase on clinical trials with an overall thrombosis rate of 34% when no AT replacement was prescribed. Elliott, et al demonstrated an overall incidence of 18.5% asparaginase-related thrombosis in a retrospective comparative analysis of adult ALL patients receiving asparaginase-containing combination chemotherapy, with all events occurring in the group without replacement. Lastly, Hunault-Berger, et al retrospectively analyzed 214 pediatric and adult ALL patients and found a 9.3% overall incidence of thrombosis. Once again, there was a higher incidence of thrombosis in patients who did not receive AT replacement.

Most of the evidence surrounding thromboprophylaxis involves pediatric ALL patients and is currently inconclusive. Mitchell and colleagues conducted the only prospective randomized analysis of replacing AT in pediatric ALL patients and screening for subsequent thromboembolic events.[13] The study was underpowered to detect a true difference in efficacy and safety and could only report trends in these outcomes.[9] The incidence of thrombosis in patients treated with AT was 28% (CI 10–46%) versus 37% (24–49%) in the non-treated arm. There was no difference in hemorrhagic events. The high overall event rate was attributed to the routine intensive asymptomatic screening process.[9]

Pre-emptive replacement of AT has no prospective evidentiary support in adults, though numerous small retrospective cohort studies have seen in vitro improvement in coagulation parameters.[7,14] Unfortunately, small sample size and variability in replacement parameters has limited generalizability of these results, particularly with the newer pegylated formulation of asparaginase.[7,10,15,16] There was no association between the target AT activity level and the risk of thrombosis with different targets for replacement (80% vs. 100%), questioning the optimal threshold for replacement initiation as well as target replacement goals. The median AT activity level at time of TE in our study was 58%; however, the small number of events precludes analysis surrounding the threshold values between those that did and did not have an event. We also performed modeling utilizing “days under threshold replacement value” and “area under the replacement value” as an index to predict thrombosis; however, an association was not found. This is similar to other studies evaluating laboratory parameters in attempt to account for duration and intensity below the respective critical thresholds, represented as a “d-index” and “l-index”, which also failed to find any association.[17–20] We felt that this analysis was the most appropriate given the longitudinal observation of patients undergoing chemotherapy for such an extended period of time. The time under the threshold replacement indicates how difficult it is to keep patients within a planned therapeutic index and demonstrates the need to investigate and determine an optimal monitoring and supplementation strategy when prescribing AT replacement. Similarly, most events occurred during the induction phase of chemotherapy questioning the necessity of employing such strategies in other phases of treatment.

The paucity of data for adult ALL patients has led practitioners to formulate management strategies from recommendations based on expert opinion.[8] Studies investigating the use of fresh frozen plasma, cryoprecipitate, AT concentrates, low molecular weight heparin, and low molecular weight heparin in combination with ATIII concentrate exist suggesting potential benefit from thromboprophylaxis in adult ALL patients during asparaginase therapy.[4,7,21] Conversely, other research has either concluded that replacement strategies may be unwarranted or left many questions unanswered due to the significant limitations of the investigation including small sample size, retrospective design or heterogeneity in supportive prophylaxis strategy.[22–24]

Expenditures for ALL are relative to both the expense of the regimen utilized, cost of life years saved (LYS) and the management of complications. A cost effectiveness analysis of protocol ALL9 versus ALL10 in pediatric ALL evaluated advancements including the monitoring of minimal residual disease and inclusion of PEGASP. While the mean total cost increased nearly 50,000 USD/patient, the authors concluded that the difference between costs in LYS, 1962 USD in ALL9 and 2655 USD in ALL10, respectively, was nominal compared to cost per LYS for adult acute leukemia patients undergoing post-remission consolidation chemotherapy at 11,224 USD.[25] A pharmacoeconomic analysis was performed comparing the drug costs of pegaspargase and *E. coli* L-asparaginase when administered in three common ALL combination chemotherapy treatment protocols. Results demonstrated considerable cost savings when pegaspargase was prescribed.[19] A subsequent pharmacoeconomic analysis in 2002 evaluated administration of LASP vs PEGASP in pediatric patients on protocol CCG 1962. This analysis included greater societal burden details such as transportation, lodging, and missed work days while also accounting for cost per clinic visit and cost per inpatient hospital day. They found PEGASP cost to only be 1.8% more than LASP and recommended substitution for patient convenience.[25] The results of these comparisons are limited by several factors including focus on direct drug expenditure and the incidence of hypersensitivity reactions. Our examination of supportive measures with AT replacement found considerably more expense than with isolated, chemotherapy acquisition costs; however, this reflects real world treatment and provides insight into potential costs encompassed within total patient supportive management. Interestingly, in a pediatric ALL study, the median estimated expenditures on AT supplementation with fresh frozen plasma was less than the amount required to treat high-risk patients affected by central nervous system thrombosis (CNST).[24] The minimum total cost to care for patients who had a CNST was 134,197 Canadian dollars while prevention of such an event would amount to half of that cost (65,088 Canadian dollars).[24] Future research is needed to determine an optimal AT activity monitoring and AT supplementation strategy..

Limitations of this study include its retrospective design and sample derived from a single center. We attempted to overcome this by including all patients regardless of malignancy, chemotherapy regimen, or asparaginase product formulation. This represents a real-world population and the heterogeneity of the regimens and dosing schema reflect the variety of investigational clinical trials conducted at our institution. Additionally, the pegylated formulation wasn't available at the beginning of the study's timeframe but has replaced L-asparaginase as the frontline agent of investigation in the treatment of adult ALL. Second is

the heterogeneity with which antithrombin levels were measured; however, strong adherence to our aforementioned institutional protocol with predefined replacement thresholds demonstrated uniformity across patients and their respective providers. Third, all events were symptomatic and radiologic imaging was performed to confirm suspected events which may have led to an underestimation of event occurrences compared to the methodology that employed radiologic evaluation at systematic time points for surveillance. Additionally, our patients were all provided AT supplementation preventing comparative analysis to determine whether thromboprophylaxis during LASP or PEGASP therapy provides a true benefit; however, our comparison of two different AT replacement thresholds and AT targets is clinically useful and serves as a benchmark for future investigations. Nevertheless, we feel the characterization of thrombotic events in our adult ALL patient population contributes to the growing body of literature regarding thromboprophylaxis in an at-risk patient population. The inclusion of estimated cost expenditures provides insight to the economic impact of AT supplementation following asparaginase administration, particularly PEGASP.

Conclusion

Prevention of thrombotic events related to asparaginase administration is an important consideration during treatment of malignancy, especially during induction or initial salvage therapy, as schedule delays or agent omission may adversely impact overall survival. Our results demonstrate, in the absence of routine imaging, a small incidence of non-LRDVT (n=3) with the use of AT supplementation following asparaginase therapy. Modification of AT thresholds and targets did not adversely impact thrombotic events. As intensive asparaginase administration with the pegylated formulation remains at the forefront of investigation for the treatment of adult ALL, AT replacement to prevent thrombosis with optimal dose, schedule, thresholds and target activity levels requires rigorous prospective, comparative evaluation. Additionally, economic analysis is necessary to determine the cost-effectiveness of AT replacement as a supportive measure.

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Figure 1.

Cumulative incidence of thrombosis in adult cancer patients receiving L-asparaginase(LASP) or pegylated asparaginase(PEGASP) containing chemotherapy between 1/2000 and 6/2016 stratified by target AT activity level goal.

Figure 2.

Median cost estimates of antithrombin concentrate per chemotherapy regimen according to Centers for Medicare & Medicaid Services pricing expressed per 1,000 USD and adjusted to 2016 USD. One patient who received C10403 was an extreme outlier (544,699 USD adjusted to 2016-ASP) and was excluded from this figure.

Table I

Baseline demographics and clinical characteristics of adult patients receiving AT supplementation following asparaginase-containing combination chemotherapy at Mayo Clinic Hospital, Rochester between 2000 and 2016

Baseline Demographic and clinical characteristic	Total Patients (n=92)	Target AT activity of 100% (n=78)	Target AT activity of 80% (n=14)	p-value
Male, No. (%)	51 (55)	42 (54)	9 (64)	0.47
Age (years), median (IQR)	41 (26–57)	40 (26–55)	54 (29–60)	0.24
Body Surface Area, m ² , median (IQR)	2.0 (1.8–2.1)	2.0 (1.8–2.1)	1.9 (1.8–2.3)	0.41
Race, No. (%)				0.68
Caucasian	79 (86)	66 (85)	13 (93)	
Non-Caucasian	13 (14)	12 (15)	1 (7)	
Social History, No. (%)				
Smoking	31 (34)	29 (37)	2 (14)	0.13
Alcohol Use	38 (41)	34 (44)	4 (29)	0.38
Malignancy diagnosis, No. (%)				0.11
B-cell lymphoblastic leukemia/lymphoma	26 (28)	19 (25)	7 (50)	
B-cell lymphoblastic leukemia, NOS	27 (29)	26 (33)	1 (7)	
T-cell lymphoblastic leukemia/lymphoma	27 (29)	23 (30)	4 (29)	
NK/T-cell lymphoma	6 (7)	4 (5)	2 (14)	
Acute Myelogenous Leukemia	5 (6)	5 (6)	0 (0)	
Diffuse large B-cell Lymphoma	1 (1)	1 (1)	0 (0)	
Primary Diagnosis, No. (%)				0.45
New diagnosis	53 (58)	47 (60)	6 (43)	
First relapse	28 (30)	22 (28)	6 (43)	
More than 1 relapse	11 (12)	9 (12)	2 (14)	
B-cell Philadelphia Chromosome status				0.42
Positive, No. (%)	38 (72%)	31 (69)	7 (87)	
Negative, No. (%)	15 (28%)	14 (31)	1 (13)	
Baseline Lab Values, median (IQR)				
White blood cell count, ×10 ⁹ /L	6.3 (2.6–15.6)	6.0 (2.5–13)	13.4 (6–24.8)	0.13
Absolute neutrophil count, ×10 ⁹ /L	1.7 (0.6–4.3)	1.6 (0.6–3.8)	2.6 (1.1–5.6)	0.37
Absolute lymphocyte count, ×10 ⁹ /L	1.2 (0.7–2.3)	1.3 (0.8–2.2)	0.9 (0.4–2.3)	0.43
Hemoglobin, g/dL	10.4 (9–12.7)	10.1 (8.7–12.5)	12.3 (11–13.5)	0.01
Platelets, ×10 ⁹ /L	71 (36–159)	63 (30–140)	99 (44–245)	0.17
Activated partial thromboplastin time, sec	28 (25–33)	28 (25–33)	30 (29–34)	0.11
Fibrinogen, mg/gL	357 (282–483)	359 (280–495)	331 (289–463)	0.76
AT activity, (%)	99 (89–110)	100 (88–109)	95 (92–119)	0.45

Baseline Demographic and clinical characteristic	Total Patients (n=92)	Target AT activity of 100% (n=78)	Target AT activity of 80% (n=14)	p-value
D-Dimer, mg/L	775 (353–1698)	815 (415–1900)	435 (260–625)	0.24
Lactate dehydrogenase, units/L	367 (237–594)	392 (247–598)	295 (228–498)	0.51
Serum creatinine, mg/dL	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.9 (0.7–1.2)	0.68
Aspartate Aminotransferase, Units/L	31 (22–64)	32 (22–65)	27 (21–37)	0.29
Alanine Aminotransferase, Units/L	36 (23–64)	40 (24–68)	30 (14–41)	0.08
Total Bilirubin, mg/dL	0.5 (0.3–0.7)	0.5 (0.3–0.8)	0.4 (0.3–0.5)	0.12

Table II

Regimens utilizing LASP or PEGASP, dosing schemes and patient frequencies at Mayo Clinic Hospital, Rochester between 2000 and 2016

Regimen	Patient Eligibility	Phase or duration	Dose (Cycle days)	Total Patients (n=92)	Target AT activity 100% (n=78)	Target AT activity 80% (n=14)
Augmented HyperCVAD	Frontline and relapse	8 cycles	LASP 20000 Units (1, 8, 15) PEGASP 1000–2000 Units/m ² (1)	13 (14)	8 (10)	5 (36)
ECOG 2993	FrontlineOnly	Induction	LASP 10000 Units (17–28) PEGASP 2500 Units/m ² (5, 22)	18 (20)	18 (23)	0 (0)
		Intensification	LASP 10000 Units (2, 9, 23) PEGASP 2500 Units/m ² (2, 23)			
CCG 1941	Frontline and relapse	Induction	PEGASP 2000 Units/m ² (2, 16)	8 (9)	8 (10)	0 (0)
		Intensification (5 cycles)	PEGASP 2000 Units/m ² (5)			
CALGB 9111	Frontline and relapse	Course I	LASP 6000 Units/m ² (4, 7, 11, 15, 18, 22) PEGASP 2000 Units/m ² (5, 22)	21 (23)	21 (27)	0 (0)
		Course II	LASP 6000 Units/m ² (15, 18, 22, 25, 43, 46, 50, 53) PEGASP 2000 Units/m ² (15, 43)			
CALGB 10403 *	Frontline	Induction ± Extension	PEGASP 2500 Units/m ² (4)	13 (14)	10 (13)	3 (22)
		Consolidation	PEGASP 2500 Units/m ² (15, 43)			
		Interim Maintenance	PEGASP 2500 Units/m ² (2, 22)			
		Delayed Intensification	PEGASP 2500 Units/m ² (4, 43)			
ECOG 1910	Frontline	Induction (Arm A)	C1: PEGASP 2000 Units/m ² (18) C2: PEGASP 2000 Units/m ² (15)	2 (2)	0 (0)	2 (14)
		Intensification (Arm B)	PEGASP 2000 Units/m ² (9)			
		Consolidation (Arms C/D)	C1: PEGASP 2000 Units/m ² (5)			
Capizzi II	Relapse	Induction	PEGASP 2000 Units/m ² (2)	12 (13)	10 (13)	2 (14)
Modified SMILE	Frontline or Relapse	Induction	PEGASP 2000 Units/m ² (8)	5 (5)	3 (4)	2 (14)

* Investigative regimen did not specify or involve any dose capping

Table III
agic events observed during administration of asparaginase chemotherapy followed by thromboprophylaxis with AT.

Line type	BMI / BSA	Current Smoker Status	Immuno-phenotype	Target AT level	Protocol	Outcome source	Imaging	ASP product	Total ASP units prior to thrombus	Days from last ASP dose to event	Days from last AT replacement to event	AT activity level on day of event
PICC	40 / 2.3	No	T-cell	100	CCG 1941	LRDVT	U/S	PEGASP	1900	15	7	NR
PICC	29 / 1.9	Yes	B-cell	100	ECOG 2993	LRDVT	U/S	PEGASP	1875	16	3	60%
HM	27 / 1.8	No	B-cell	100	ECOG 2993	LRDVT	U/S	LASP	4000	4	1	65%
PICC	30 / 1.8	No	B-cell	100	ECOG 2993	LRDVT	U/S	LASP	12000	56	56	NR
PICC	20 / 1.6	No	B-cell	100	Augmented HyperCVAD	LRDVT	U/S	LASP	8000	3	10	NR
HM	26 / 2.3	No	T-cell	100	ECOG 2993	PE	CT	LASP	132000	12	1	56%
PICC	37 / 2.4	No	B-cell	100	CALGB 10403	LRDVT	U/S	PEGASP	29850	22	2	72%
HM	31 / 2.0	No	B-cell	100	CALGB 9111	CVST	MRI	LASP	48720	3	1	47%
PICC	35 / 2.3	No	T-cell	100	CCG 1941	LRDVT	U/S	PEGASP	3750	13	3	51%
PICC	22 / 1.8	No	B-cell	100	CALGB 9111	LRDVT	U/S	PEGASP	4400	10	1	NR
PICC	23 / 1.7	Yes	T-cell	100	ECOG 2993	Superficial thrombophlebitis	U/S	LASP	12000	10	10	NR
PICC	27 / 2.0	Yes	N/A	100	Modified SMILE	LRDVT	U/S	PEGASP	4050	9	1	55%
PICC	27 / 2.0	Yes	N/A	100	Modified SMILE	LRDVT	U/S	PEGASP	4050	17	1	78%
PICC	29 / 2.1	No	B-cell	80	ECOG 1910	LRDVT	U/S	PEGASP	2200	4	N/A	57%
PICC	22 / 1.5	No	N/A	80	Modified SMILE	LRDVT	U/S	PEGASP	3350	4	N/A	60%

ombin, BMI = Body Mass Index: Weight (in Kilograms) / height² (in meters), BSA (meters²) according to Gehan-George formula: 0.0235 × (Height^{0.42246} (in kilograms), CT = computed tomography, CVST = central venous sinus thrombosis, HM = Hickman[®], MRI = magnetic resonance imaging, N/A = not applicable (event not recorded), NR = not recorded, PE = pulmonary embolus, PICC = peripherally inserted central catheter, LRDVT = Line Related Deep Venous Thrombosis, PEGASP = pegylated asparaginase.