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The Frequency and Management of Asparaginase-Related Thrombosis in Paediatric and Adult Patients with Acute Lymphoblastic Leukaemia Treated On Dana-Farber Cancer Institute Consortium Protocols

Rachael F. Grace, MD^{1,2}, Suzanne E. Dahlberg, PhD^{2,3}, Donna Neuberg, ScD^{2,3}, Stephen E. Sallan, MD^{1,2}, Jean M. Connors, MD^{2,4}, Ellis J. Neufeld, MD, PhD^{1,2}, Daniel J. DeAngelo, MD, PhD^{2,4}, and Lewis B. Silverman, MD^{1,2}

¹Pediatric Hematology/Oncology, Children's Hospital Boston, Dana-Farber Cancer Institute, Boston, MA

²Harvard Medical School, Boston, MA

³Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA

⁴Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

SUMMARY

The optimal management of asparaginase-associated thrombotic complications is not well-defined. We report the features, management, and outcome of paediatric (ages 0–18 years) and adult (18–50 years) patients with acute lymphoblastic leukaemia (ALL) with asparaginase-related venous thromboembolic events (VTE) treated at Dana-Farber Cancer Institute on clinical trials for newly diagnosed ALL between 1991–2008. Of 548 patients, 43 (8%) had VTE, including 27/501 (5%) paediatric and 16/47 (34%) adult patients. Sinus venous thrombosis occurred in 1.6% of patients. Age was the only significant predictor of VTE, with those aged >30 years at very high risk (VTE rate 42%). 74% of patients received low molecular weight heparin after VTE. Complications of anticoagulation included epistaxis (9%), bruising (2%), and, in two adult patients, major bleeding. 30 patients (70%) ultimately received at least 85% of the intended doses of asparaginase. 33% of patients experienced recurrent VTE (paediatric 17% vs. adults 47%, $p=0.07$). The 48-month event-free survival for patients with VTE was $85 \pm 6\%$ compared with $88 \pm 2\%$ for those without VTE ($p=0.36$). This study confirms that, after VTE, asparaginase can be restarted with closely monitored anticoagulation after imaging demonstrates clot stabilization or improvement. With this management strategy, a history of VTE does not appear to adversely impact prognosis.

Correspondence: Rachael F. Grace, MD, Children's Hospital Boston, 300 Longwood Avenue, Karp 8, Boston, Massachusetts 02115, Rachael.Grace@childrens.harvard.edu, Phone: 617-919-2144, Fax: 617-730-0934.

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Keywords

acute lymphoblastic leukaemia; asparaginase; thrombosis; anticoagulation; management

INTRODUCTION

Asparaginase-related thrombosis is a significant complication of acute lymphoblastic leukaemia (ALL) therapy in children and adults (Mitchell *et al*, 1994a, b, Mitchell *et al*, 2003, Priest *et al*, 1982). The anti-leukaemia effect of asparaginase, a critical component of ALL treatment, is related to asparagine depletion (Carlsson *et al*, 1995, Nowak-Gottl *et al*, 1996a, b). Prolonged asparagine depletion is also associated with the development of coagulation defects (Duval *et al*, 2002, Mitchell *et al*, 1994b, 1995). In patients with ALL and a thrombotic complication, the goal of adequately treating venous thromboembolic events (VTE) to prevent extension or recurrence must be balanced with the primary goal of maximizing exposure to asparaginase to successfully treat the leukaemia.

The reported incidence of VTE in patients with ALL ranges from 1% to 36% depending upon the treatment protocol, whether asymptomatic events are included, and whether the study design was prospective or retrospective (Mitchell *et al*, 2003, Nowak-Gottl *et al*, 2001, 2009, Payne and Vora 2007, Silverman *et al*, 2001, Sutor *et al*, 1999). Increased risk of thrombosis in patients with ALL has been ascribed to multiple factors, including leukaemia burden, the presence of central venous catheters, genetic predisposition, and treatment-induced coagulation defects, especially by asparaginase (Andrew *et al*, 1994, Mitchell *et al*, 1994b). While the increased risk of VTE in individuals with ALL has long been recognized, few studies focus on the management and outcomes of individuals with ALL and thrombotic complications, especially in the adult population.

Current adult and paediatric ALL treatment regimens often do not provide specific guidelines for the management of asparaginase-associated VTE, the role of radiographic imaging, whether to continue asparaginase, and the method and duration of anticoagulation. We describe the management and outcome of children and adults with ALL who developed VTE while receiving asparaginase on Dana-Farber Cancer Institute (DFCI) ALL consortium protocols.

METHODS

Patient Population

Between 1991 and 2008, 501 paediatric patients (ages 0 to <18 years) with newly diagnosed ALL were enrolled on four consecutive DFCI Childhood ALL Consortium protocols (Protocols 91-01, 95-01, 00-01, and 05-01) at DFCI/Children's Hospital Boston. Between 2001 and 2008, 47 adult patients with newly diagnosed ALL were enrolled on the DFCI ALL Consortium Protocol 01-175 at DFCI/Brigham and Women's Hospital. Patients who achieved complete remission at the end of induction therapy were included in this analysis. The Institutional Review Board approved each protocol prior to patient enrollment and

approved the medical record review of patients with VTE for this analysis. Informed consent was obtained from patients, parents, or guardians before therapy started.

All cases of VTE were identified prospectively by clinical signs and symptoms and confirmed by radiological imaging based on institutional guidelines. No screening for asymptomatic clots was performed in any of the five treatment protocols. Asymptomatic central venous line (CVL) and right atrial thromboses diagnosed by imaging obtained for other purposes were excluded from this study. Only VTE that occurred between the first dose of asparaginase and 8 weeks after the final dose of asparaginase were included in the analysis. Medical records and imaging studies of all patients were reviewed retrospectively to assess symptoms at presentation, laboratory data, radiological findings, clinical course, and treatment.

Treatment Regimen on DFCI Consortium Protocols

Details of therapy on DFCI ALL Consortium protocols have been previously published (DeAngelo *et al*, 2007, Moghrabi *et al*, 2007, Silverman *et al*, 2001, 2010a, 2010b, Vrooman *et al*, 2010). Each protocol consisted of three main phases of treatment: remission induction (including 0–1 dose of asparaginase), intensification therapy (including 20–30 consecutive weeks of asparaginase), and continuation therapy (no asparaginase). Treatment for paediatric patients was stratified based on risk group assignment, as previously reported. Standard-risk patients met all of the following criteria: ages 1–10 years (2–9 years on Protocol 91-01), presenting white blood cell (WBC) count $<50 \times 10^9/l$ ($<20 \times 10^9/l$ on Protocol 91-01), B-precursor phenotype, absence of anterior mediastinal mass, and absence of central nervous system leukaemia at diagnosis (Silverman *et al*, 2001, 2010a, 2010b). All other paediatric patients were considered high-risk. Adult patients were treated similarly to high-risk paediatric patients and considered high risk for this analysis. The differences between protocols with respect to asparaginase administration are listed in Table I. There were no differences in type or total doses of asparaginase on any protocol based on risk group.

Statistical Analysis

Baseline patient demographics, disease characteristics, laboratory data, radiological findings, and clinical course results were compared using Fisher's exact test for categorical data and the Kruskal-Wallis test for continuous data. The Jonckheere-Terpstra test was used to test for a trend in risk of VTE by age. Time-to-event analyses comparing the outcomes of those with VTE to those without VTE were estimated using the Kaplan-Meier method in a landmark analysis measured from the time of the latest VTE at 0.84 years (10.1 months). Overall survival was defined as the time from the landmark time to death from any cause. Event-free survival (EFS) was defined as the time interval from the landmark time to documented relapse or death. All p-values are two-sided (with $p < 0.05$ considered significant), confidence intervals are at the 95% level, and no adjustments have been made for multiple comparisons.

RESULTS

Population Characteristics

Number of VTE in each group—A total of 48 clots were diagnosed in 43 (8%) patients during treatment phases that included asparaginase. VTE was diagnosed in 27 paediatric patients (5.4% of all paediatric patients) and 16 adults (34%). Despite the differences in the form of asparaginase (Table I) in our paediatric protocols, the incidence of VTE was similar across protocols. The presenting features of paediatric and adult patients with and without VTE are provided in Table II.

Predictors of thrombosis—Univariate predictors of VTE included high risk group, older age at diagnosis, and T-cell phenotype (Table II). In paediatric patients younger than 10 years of age, the rate of thrombosis in standard risk patients (3%) was not significantly different than the rate of thrombosis in high-risk patients (3%, $p=1.0$). There were no differences by sex, race/ethnic group, gender, mean presenting WBC count, and presence of an anterior mediastinal mass. In the multivariate model, after adjusting for the significant univariate predictors, age was the only significant predictor of VTE with the odds ratio (OR) of VTE increasing with age ($p<0.001$; Table III).

Sites and symptoms of clots—The most common sites of VTE included CVL-related/upper extremity ($n=17$), lower extremity ($n=9$), and sinus venous thrombosis ($n=9$). Seven patients experienced a pulmonary embolism. The sites of VTE were similar in adults and paediatric patients, although there was a trend for the adults to experience more pulmonary emboli and for the paediatric patients to experience more sinus venous thromboses (Table IV).

The most common symptoms from CVL-related/upper extremity VTE were upper extremity pain and swelling and/or CVL dysfunction. Lower extremity VTE presented as lower extremity swelling and/or pain. The sinus venous thromboses most often presented with headache, seizure, or neurological changes. The patients with pulmonary embolism most commonly presented with chest pain, although two patients were diagnosed incidentally.

Timing—VTE occurred during induction in 8 patients (5 adults, 3 paediatric patients) and post-induction in 35 patients. Median time to VTE was 3.5 months (0.5–10.1 months) from initiation of therapy with no difference in timing between adult and paediatric patients.

Initial Laboratory and Radiological Findings

Of the 43 patients with VTE, 29 had a laboratory evaluation for an inherited or acquired thrombophilia. Paediatric patients were more likely than adults to have at least one laboratory test performed ($p=0.02$). The most common tests performed were antithrombin III (AT) activity levels, activated protein C resistance (APC-R), and the *F2* (prothrombin) G20210A gene mutation. AT activity levels, protein C activity levels, protein S activity levels, factor VIII activity levels, and/or D-dimer levels were abnormal in 30% of those individuals tested. Of 23 patients tested for either APC-R or a *F5*R506Q (Factor V Leiden) mutation, 2 (9%) screened positive for APC-R, of whom 1 (4%) was confirmed to have *F5*

R506Q mutation, similar to that expected for the general population. Of 17 patients screened for a *F2G20210A* mutation, 2 (12%) were positive, similar to that expected in the general population.

All cases of VTE were confirmed by radiological imaging including 51 imaging studies obtained in the 43 patients at the time of VTE diagnosis. The majority was imaged using ultrasound or computed tomography.

Anticoagulation Management and Complications

Of the 43 patients with symptomatic VTE, 32 (74%) were initially treated with low-molecular weight heparin (LMWH) and 8 (19%) were treated with warfarin. There was no significant difference in anticoagulation therapy between paediatric and adult patients. Patients treated in the 1990s were more likely to have received warfarin compared with those treated on more recent protocols. Two patients with sinus venous thrombosis did not receive anticoagulation or further doses of asparaginase by physician choice due to post-thrombotic haemorrhage, and one patient received systemic urokinase in the setting of a symptomatic CVL-related thrombosis with resultant CVL-removal without further systemic anticoagulation.

Anti-Xa levels were followed in all paediatric patients (18/18) and in 14% (2/14) adults receiving LMWH ($p<0.01$). Goal anti-Xa levels ranged from 0.4–0.6 u/ml, in patients at higher bleeding risk due to persistent thrombocytopenia (24% of those with levels checked), and 0.5–1 u/ml in the rest of the patients (76% of those with levels checked). If the level was not in goal range, the LMWH dose was titrated until the anti-Xa level was within goal range. In the majority of paediatric patients, once in goal range, anti-Xa levels were followed at least monthly. Once anticoagulated during asparaginase therapy, antithrombin (AT) activity levels were checked in all (18/18) paediatric patients at least once weekly while on LMWH compared with 1 of 14 (7%) adults on LMWH ($p<0.01$). In those patients in whom AT levels were monitored, AT concentrate was infused when levels fell below 50–75%, with three quarters of the patients receiving infusions for levels at or below 60%. In patients treated with warfarin, half of the patients had a goal International Normalized Ratio (INR) of 1–2 and half had a goal INR of 2–3.

Complications of any anticoagulation included epistaxis (10%) and bruising (2%). Two patients (both adults) experienced major bleeding during anticoagulation with LMWH (one intracranial haemorrhage and one compartment syndrome after a bone marrow aspirate).

Anticoagulation was discontinued after completion of all planned doses of asparaginase (approximately 30–40 weeks after initial diagnosis of ALL) in 60% of paediatric patients compared with 31% of adult patients. In 38% of adult patients, anticoagulation was continued until all chemotherapy was completed (approximately 108 weeks after initial ALL diagnosis), although only 8% of paediatric patients continued anticoagulation for this prolonged period of time ($p=0.02$).

Radiographic Imaging of VTE after Starting Anticoagulation

Seventy-two percent of patients with VTE were reimaged after initiation of anticoagulation. Paediatric patients were more likely than adults to be reimaged prior to restarting asparaginase (56% vs. 6%, $p<0.01$). Paediatric patients were reimaged at a median of 3 weeks after VTE in comparison to a median of 9 weeks in adults. Of the paediatric patients who were reimaged, 96% demonstrated resolution/stabilization of the VTE, whereas 58% of reimaging in adults demonstrated resolution/stabilization ($p=0.05$). Ten percent (3/31) of reimaging of VTE showed extension of the thrombosis. Two of these patients had been restarted on asparaginase prior to reimaging.

Re-treatment with Asparaginase After VTE

Asparaginase was held in all patients after diagnosis of VTE (for a median duration of 9 weeks in paediatric patients and of 4 weeks in adults ($p=0.01$)). Asparaginase was restarted in 77% of patients with no difference between adult and paediatric patients. Of the 43 patients with VTE, 70% (30/43) received at least 85% of the intended doses of asparaginase.

Recurrence of VTE occurred only in those patients restarted on asparaginase. Of the 33 patients restarted on asparaginase after VTE, 33% (11/33) experienced a recurrence of VTE (17% of paediatric patients vs. 47% of adults, $p=0.07$). Seven of the 11 recurrences were in adult patients. There was no association between initial site of VTE and risk of clot recurrence. Of the 11 patients with VTE recurrence, only 2 had been reimaged prior to restarting asparaginase. The site of recurrence/extension tended to be the same as the site of the original thrombosis. Asparaginase was continued in 5 patients after VTE recurrence and had already been completed in the other 6 patients. Patients with recurrent VTE received an average of 96% of total intended doses of asparaginase.

Outcome and Prognosis

Complications from the first VTE included postphlebotic syndrome (7%), neurological changes (ranging from chronic headaches to seizures (20%)), catheter removal (21%), and prematurely discontinuing asparaginase (14%) (Table V). There were no deaths directly related to VTE. Adults had a higher rate of postphlebotic syndrome from the first VTE than paediatric patients ($p=0.05$), but the other complications occurred with similar frequencies. With a median follow-up of 52 months, the 48-month EFS and overall survival (OS) for patients with VTE was $85\% \pm 6\%$ and $86\% \pm 7\%$, respectively. The 48-month EFS and OS for the patients without VTE was $88\% \pm 2\%$ and $95\% \pm 1\%$, respectively. There was no significant difference in EFS ($p=0.36$) or OS ($p=0.12$) when comparing patients with and without VTE.

DISCUSSION

In our series, in which patients with ALL aged 0–50 years were treated with a uniform chemotherapy regimen, 5% of paediatric patients and 34% of adult patients with ALL experienced thrombosis during the treatment phases that included asparaginase. Our data clearly shows that thrombotic risk due to asparaginase increases with age, with those aged >10 years at high risk and those aged >30 years at extremely high risk for VTE. After

VTE, asparaginase was restarted with concurrent anticoagulation in 77% of patients, of whom 33% had VTE recurrence. Anticoagulation was associated with few bleeding complications. Although significant morbidity was associated with VTE regardless of age, most patients were ultimately able to receive nearly all of their intended doses of asparaginase. The occurrence of VTE did not appear to adversely impact EFS or OS.

The 5.4% incidence of symptomatic thrombotic events in children was similar to previous reports, including a 5.2% incidence from a meta-analysis of 1752 paediatric patients on 17 different trials, many of which included fewer doses of asparaginase (Athale *et al*, 2005, Caruso *et al*, 2006, Nowak-Gottl *et al*, 2009, Payne and Vora 2007). Fewer reports describe the rate of thrombotic complications in adults receiving asparaginase-intensive ALL therapy (Caruso *et al*, 2007, Elliott *et al*, 2004, Gugliotta *et al*, 1992, Hunault-Berger *et al*, 2008, Ku *et al*, 2009, Mohren *et al*, 2006). The variation in incidence of previously reported VTE complications during ALL therapy may be explained by differences in the intensity of asparaginase (the dose and type) and other chemotherapy, whether patients were screened for asymptomatic VTE, the range of ages of the patients, and the design of the study. The thrombotic events in our study were reported prospectively and may have been more easily identified than in those studies in which thrombotic events are identified retrospectively. For instance, in the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) adult ALL 0288 trial, the rate of thrombosis was only 4.2%, but the fatality rate in these cases was 50% (Gugliotta *et al*, 1992). This elevated fatality rate may reflect a bias in reporting major thrombotic events. In our series, there were no deaths related to VTE.

Previous studies in paediatric ALL patients have demonstrated that adolescents are at higher risk for VTE than younger children (Barry *et al*, 2007, Caruso *et al*, 2006). In the past, comparing rates of VTE in paediatric and adult patients has been difficult due to differences in therapy. Our study is the first to report the risk of thrombosis across the ALL age spectrum. We clearly demonstrated that thrombotic risk due to asparaginase increases with age. In this series, patients aged 10–50 years were treated with nearly identical therapy, and the dosing of asparaginase was the same for all patients, regardless of age. Thus, we were able to control for any treatment-related factors and clearly demonstrated the increasing VTE risk with age. The current study emphasizes the importance of age in the development of VTE, with the frequency of VTE increasing along the age continuum from 2% (ages 0–5 years) to 20% (ages 11–14 years) to 42% (age >30 years). Other investigators have shown that, in general, younger children are at lower risk for thrombosis than adolescents and adults (Monagle *et al*, 2006). In paediatric patients with ALL undergoing asparaginase therapy, it has been shown that older children have both decreased anticoagulant factors and decreased fibrinolysis in comparison to younger children receiving identical therapy (Appel *et al*, 2008). These same mechanisms are potentially accentuated across the age spectrum and help to explain the increasing frequency of VTE with age in our series.

In addition to being at higher risk for VTE occurrence, adults were also at higher risk for VTE recurrence. Two main differences were identified in the management of the paediatric versus adult patients in this study: 1) paediatric patients were much more likely to undergo reimaging prior to restarting asparaginase, and 2) paediatric patients were much more likely to have anti-Xa levels checked and antithrombin repleted during treatment with LMWH.

Whether these management differences played a role in the higher thrombosis recurrence rate in adults cannot be determined from the available data. Given that the risk of thrombosis is much higher overall in adults than children, factors unrelated to VTE management may have also contributed to the higher recurrence rate in adult patients.

AT levels were followed in most paediatric patients receiving LMWH. The requirement of AT for adequate anticoagulation with heparin is well described (Kuhle *et al*, 2006, Monagle *et al*, 2008). As heparin's anticoagulant effect works by potentiating AT-mediated inhibition of coagulant enzymes, the presence of adequate AT is necessary for heparin to have any anticoagulant effect (Rodgers 2009). Asparaginase is known to deplete AT; thus, patients receiving asparaginase may have inadequate anticoagulation with heparin as a result of low AT levels. However, it is not clear whether AT needs to be monitored in all asparaginase-treated patients or only those with sub-therapeutic anti-Xa levels.

Few paediatric patients experienced a bleeding complication while on anticoagulation, demonstrating the feasibility of administering these medications during treatment for ALL. These results are consistent with the findings of others, including a meta-analysis of 17 prospective studies of thrombotic complications in paediatric patients with ALL that found a 2% overall incidence of bleeding complications (Caruso *et al*, 2006, Meister *et al*, 2008, Qureshi *et al*, 2010). The frequency of bleeding complications in adult ALL patients on anticoagulation has not been as well characterized. In our study, 2 (12.5%) adult patients had significant bleeds with anticoagulation.

There is a paucity of data regarding the safety of resuming asparaginase after VTE. It is challenging to balance the goal of effectively treating leukaemia by administering all intended asparaginase doses with that of minimizing morbidity and mortality from thrombotic complications, especially in patients who have already experienced thrombosis. Two previous reports demonstrated a lower EFS in patients with VTE, which may have been due to early discontinuation of asparaginase (Hunault-Berger *et al*, 2008, Ku *et al*, 2009). We have previously reported that early discontinuation of asparaginase due to toxicity is associated with an inferior EFS in paediatric patients (Silverman *et al*, 2001). Therefore, nearly all patients were re-challenged with asparaginase after a thrombotic episode, typically after several weeks of anticoagulation therapy. With this strategy, 70% of patients received at least 85% of their intended doses of asparaginase and, importantly, had similar EFS and OS rates compared with patients treated on the same regimen who did not experience thrombotic complications.

Randomized trials of VTE management in patients with ALL are challenging to design and implement, due to the low overall incidence of patients with this complication. Therefore, development of evidence-based guidelines for the treatment of these individuals is difficult. Although the results of this study are limited by their retrospective nature, our findings might help to provide the foundation for such guidelines.

Based on the similar EFES and OS rates in patients with and without VTE in our study, we recommend our management strategy of re-challenging with asparaginase after first VTE. We believe that a reasonable approach to such patients is as follows: patients with first VTE

should be diagnosed with radiological imaging and then anticoagulation should be started. CVL removal should be considered if the line is nonfunctional or causing symptoms that do not resolve with anticoagulation. Asparaginase can be resumed when VTE symptoms have resolved and there is evidence of clot stabilization and/or improvement on repeat imaging. In our experience, the typical time frame until asparaginase can be restarted is about 4 weeks. Given that patients on asparaginase have significant protein depletion, anti-Xa levels should be monitored regularly in all age groups during anticoagulation while on asparaginase. If LMWH at previously adequate doses does not anticoagulate the patient, antithrombin activity levels should be checked and repleted as necessary to maintain goal anti-Xa levels.

Thus, we feel that asparaginase can safely be administered in the setting of concurrently administered anticoagulation in patients with ALL who have VTE. Recurrence of thrombotic events during asparaginase therapy might be minimized by following anti-Xa levels and repleting AT during heparin-based therapy. Individuals older than 30 years with ALL are at very high risk for developing thrombotic complications during asparaginase treatment and might benefit from interventions designed to prevent VTE, such as prophylactic dosing of anticoagulant medications. Prospective studies are needed to determine optimal management of patients to prevent and treat asparaginase-associated VTE.

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References

- Andrew M, Brooker L, Mitchell L. Acquired antithrombin III deficiency secondary to asparaginase therapy in childhood acute lymphoblastic leukaemia. *Blood Coagul Fibrinolysis*. 1994; 5(Suppl 1):S24–36. discussion S59–64. [PubMed: 8186353]
- Appel IM, Hop WC, van Kessel-Bakvis C, Stigter R, Pieters R. L-Asparaginase and the effect of age on coagulation and fibrinolysis in childhood acute lymphoblastic leukemia. *Thromb Haemost*. 2008; 100:330–337. [PubMed: 18690355]
- Athale UH, Siciliano SA, Crowther M, Barr RD, Chan AK. Thromboembolism in children with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute protocols: effect of age and risk stratification of disease. *Br J Haematol*. 2005; 129:803–10. [PubMed: 15953008]
- Barry E, DeAngelo DJ, Neuberg D, Stevenson K, Loh ML, Asselin BL, Barr RD, Clavell LA, Hurwitz CA, Moghrabi A, et al. Favorable outcome for adolescents with acute lymphoblastic leukemia treated on Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocols. *J Clin Oncol*. 2007; 25:813–9. [PubMed: 17327603]
- Carlsson H, Stockelberg D, Tengborn L, Braide I, Carneskog J, Kutti J. Effects of Erwinia-asparaginase on the coagulation system. *Eur J Haematol*. 1995; 55:289–93. [PubMed: 7493674]
- Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Mariani G, de Gaetano G, Donati MB. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. *Blood*. 2006; 108:2216–22. [PubMed: 16804111]

- Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Donati MB. Venous thrombotic complications in adults undergoing induction treatment for acute lymphoblastic leukemia: results from a meta-analysis. *J Thromb Haemost*. 2007; 5:621–3. [PubMed: 17229043]
- DeAngelo DJ, Dahlberg SE, Silverman L, Couban S, Amrein PC, Setfel MD. A Multicenter Phase II Study Using a Dose Intensified Pediatric Regimen in Adults with Untreated Acute Lymphoblastic Leukemia. *Blood (ASH Annual Meeting Abstracts)*. 2007; 110:587.
- Duval M, Suciu S, Ferster A, Rialland X, Nelken B, Lutz P, Benoit Y, Robert A, Manel AM, Vilmer E, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. *Blood*. 2002; 99:2734–9. [PubMed: 11929760]
- Elliott MA, Wolf RC, Hook CC, Pruthi RK, Heit JA, Letendre LL, Tefferi A, Kaufmann SH, Mesa RA, Litzow MR. Thromboembolism in adults with acute lymphoblastic leukemia during induction with L-asparaginase-containing multi-agent regimens: incidence, risk factors, and possible role of antithrombin. *Leuk Lymphoma*. 2004; 45:1545–9. [PubMed: 15370205]
- Gugliotta L, Mazzucconi MG, Leone G, Mattioli-Belmonte M, Defazio D, Annino L, Tura S, Mandelli F. Incidence of thrombotic complications in adult patients with acute lymphoblastic leukaemia receiving L-asparaginase during induction therapy: a retrospective study. The GIMEMA Group. *Eur J Haematol*. 1992; 49:63–6. [PubMed: 1397242]
- Hunault-Berger M, Chevallier P, Delain M, Bulabois CE, Bologna S, Bernard M, Lafon I, Cornillon J, Maakaroun A, Tizon A, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. *Haematologica*. 2008; 93:1488–94. [PubMed: 18728028]
- Ku GH, White RH, Chew HK, Harvey DJ, Zhou H, Wun T. Venous thromboembolism in patients with acute leukemia: incidence, risk factors, and effect on survival. *Blood*. 2009; 113:3911–7. [PubMed: 19088376]
- Kuhle S, Lau A, Bajzar L, Vegh P, Halton J, Cherrick I, Anderson R, Desai S, McCusker P, Wu J, et al. Comparison of the anticoagulant effect of a direct thrombin inhibitor and a low molecular weight heparin in an acquired antithrombin deficiency in children with acute lymphoblastic leukaemia treated with L-asparaginase: an in vitro study. *Br J Haematol*. 2006; 134:526–31. [PubMed: 16856890]
- Meister B, Kropshofer G, Klein-Franke A, Strasak AM, Hager J, Streif W. Comparison of low-molecular-weight heparin and antithrombin versus antithrombin alone for the prevention of symptomatic venous thromboembolism in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2008; 50:298–303. [PubMed: 17443678]
- Mitchell L, Hoogendoorn H, Giles AR, Vegh P, Andrew M. Increased endogenous thrombin generation in children with acute lymphoblastic leukemia: risk of thrombotic complications in L'Asparaginase-induced antithrombin III deficiency. *Blood*. 1994a; 83:386–91. [PubMed: 8286739]
- Mitchell LG, Halton JM, Vegh PA, Barr RD, Venneri T, Pai KM, Andrew ME. Effect of disease and chemotherapy on hemostasis in children with acute lymphoid leukemia. *Am J Pediatr Hematol Oncol*. 1994b; 16:120–6. [PubMed: 8166364]
- Mitchell LG, Sutor AH, Andrew M. Hemostasis in childhood acute lymphoblastic leukemia: coagulopathy induced by disease and treatment. *Semin Thromb Hemost*. 1995; 21:390–401. [PubMed: 8747702]
- Mitchell LG, Andrew M, Hanna K, Abshire T, Halton J, Anderson R, Cherrick I, Desai S, Mahoney D, McCusker P, et al. A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. *Cancer*. 2003; 97:508–16. [PubMed: 12518376]
- Moghrabi A, Levy DE, Asselin B, Barr R, Clavell L, Hurwitz C, Samson Y, Schorin M, Dalton VK, Lipshultz SE, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007; 109:896–904. [PubMed: 17003366]

- Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A. Increased risk of venous thromboembolism in patients with acute leukaemia. *Br J Cancer*. 2006; 94:200–2. [PubMed: 16421591]
- Monagle P, Barnes C, Ignatovic V, Furmedge J, Newell F, Chan A, DeRosa L, Hamilton S, Ragg P, Robinson S, Auld A, Crock C, Roy N, Rowlands S. Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost*. 2006; 95:362–372. [PubMed: 16493500]
- Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, Michelson AD. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133(6 Suppl):887S–968S. [PubMed: 18574281]
- Nowak-Gottl U, Ahlke E, Schulze-Westhoff P, Boos J. Changes in coagulation and fibrinolysis in childhood ALL: a two-step dose reduction of one E. coli asparaginase preparation. *Br J Haematol*. 1996a; 95:123–6. [PubMed: 8857948]
- Nowak-Gottl U, Werber G, Ziemann D, Ahlke E, Boos J. Influence of two different *Escherichia coli* asparaginase preparations on fibrinolytic proteins in childhood ALL. *Haematologica*. 1996b; 81(2):127–31. [PubMed: 8641640]
- Nowak-Gottl U, Heinecke A, von Kries R, Nurnberger W, Munchow N, Junker R. Thrombotic events revisited in children with acute lymphoblastic leukemia: impact of concomitant *Escherichia coli* asparaginase/prednisone administration. *Thromb Res*. 2001; 103:165–72. [PubMed: 11672578]
- Nowak-Gottl U, Kenet G, Mitchell LG. Thrombosis in childhood acute lymphoblastic leukaemia: epidemiology, aetiology, diagnosis, prevention and treatment. *Best Pract Res Clin Haematol*. 2009; 22:103–14. [PubMed: 19285277]
- Payne JH, Vora AJ. Thrombosis and acute lymphoblastic leukaemia. *Br J Haematol*. 2007; 138:430–45. [PubMed: 17608766]
- Priest JR, Ramsay NK, Steinherz PG, Tubergen DG, Cairo MS, Sitarz AL, Bishop AJ, White L, Trigg ME, Levitt CJ, et al. A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr*. 1982; 100:984–9. [PubMed: 6953221]
- Qureshi A, Mitchell C, Richards S, Vora A, Goulden N. Asparaginase-related venous thrombosis in UKALL 2003- re-exposure to asparaginase is feasible and safe. *Br J Haematol*. 2010; 149:410–3. [PubMed: 20201945]
- Rodgers GM. Role of antithrombin concentrate in treatment of hereditary antithrombin deficiency. An update. *Thromb Haemost*. 2009; 101:806–12. [PubMed: 19404531]
- Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, Hurwitz CA, Moghrabi A, Samson Y, Schorin MA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood*. 2001; 97:1211–8. [PubMed: 11222362]
- Silverman LB, Stevenson KE, O'Brien JE, Asselin BL, Barr RD, Clavell L, Cole PD, Kelly KM, Laverdiere C, Michon B, et al. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985–2000). *Leukemia*. 2010a; 24:320–34. [PubMed: 20016537]
- Silverman LB, Supko JG, Stevenson KE, Woodward C, Vrooman LM, Neuberg DS, Asselin BL, Athale UH, Clavell L, Cole PD, et al. Intravenous PEG-asparaginase during remission induction in children and adolescents with newly diagnosed acute lymphoblastic leukemia. *Blood*. 2010b; 115:1351–3. [PubMed: 20007809]
- Sutor AH, Mall V, Thomas KB. Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr*. 1999; 211:201–4. [PubMed: 10472550]
- Vrooman LM, Supko JG, Neuberg DS, Asselin BL, Athale UH, Clavell L, Kelly KM, Laverdiere C, Michon B, Schorin M, et al. Erwinia asparaginase after allergy to E. coli asparaginase in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2010; 54:199–205. [PubMed: 19672973]

Table I

Asparaginase Dosing on DFCI ALL Consortium Protocols (1991–2008)

Protocol	Induction (28 days)	Intensification	Continuation
91-01 Paediatric	None	30 weeks of asparaginase; randomized to <i>E. coli</i> 25,000 iu/m ² weekly vs. PEG 2,500 iu/m ² every 2 weeks	None
95-01 Paediatric	1 dose: Randomized to <i>E. Coli</i> 25,000 iu/m ² vs. <i>Erwinia</i> 25,000 iu/m ²	20 weeks of asparaginase; randomized to <i>E. coli</i> 25,000 iu/m ² weekly vs. <i>Erwinia</i> 25,000 iu/m ² weekly	None
00-01 Paediatric	1 dose: <i>E. Coli</i> 25,000 iu/m ²	30 weeks of asparaginase; randomized to <i>E. coli</i> 25,000 iu/m ² weekly vs. individually-dosed <i>E. Coli</i> (dose adjusted based on nadir asparaginase enzyme levels, maximum dose 25,000 iu/m ²)	None
05-01 Paediatric	1 dose: PEG 2,500 iu/m ²	30 weeks of asparaginase; randomized to <i>E. coli</i> 25,000 iu/m ² weekly vs. PEG 2,500 iu/m ² every 2 weeks	None
01-175 Adult (18–50 years)	1 dose: <i>E. Coli</i> 25,000 iu/m ²	30 weeks of asparaginase; individually dosed <i>E. Coli</i> (dose adjusted based on nadir asparaginase enzyme levels, maximum dose 25,000 iu/m ²)	None

E. coli = *Escherichia coli* asparaginase; PEG = polyethylene glycol *Escherichia coli* asparaginase; *Erwinia* = *Erwinia* asparaginase

Table II

Presenting Features of all Patients with and without VTE

	VTE (n=43)	No VTE (n=505)	p value
Gender			
Female	16 (37%)	228 (45%)	0.34
Male	27 (63%)	277 (55%)	
Risk			
Standard	10 (23%)	240 (48%)	<0.01
High Risk *	33 (77%)	265 (52%)	
T-cell	11 (26%)	52 (10%)	0.01
Race			
White	34 (79%)	429 (85%)	0.43
Black	3 (7%)	20 (4%)	
Asian	0 (0%)	13 (3%)	
Hispanic	3 (7%)	16 (3%)	
Other	3 (7%)	27 (6%)	
Mean presenting WBC count (x 10⁹/l)	36.2	41.3	0.33
AMM	7 (16%)	43 (9%)	0.10
Age category (years)			<0.01
0–5	6 (14%)	313 (62%)	
5–10	7 (16%)	92 (18%)	
10–20	18 (42%)	77 (15%)	
20–30	4 (9%)	12 (2%)	
>30	8 (19%)	11 (2%)	
Age (median years)	14	4	<0.01

* All adults were high risk by definition.

AMM = anterior mediastinal mass, WBC = white blood cell

Table III

Odds Ratio of Developing VTE by Patient Age

Age (years)	n	VTE Rate	Odds Ratio	p value
0–5	6	2%	1	Reference group
6–10	7	7%	4.0	0.02
11–14	9	20%	12.7	<0.01
15–20	9	18%	11.7	0.01
21–30	4	25%	17.4	<0.01
>30	8	42%	37.9	<0.01

Table IV

Sites of VTE in adult and paediatric patients

	All patients n=47*	Paediatrics n=29	Adults n=18	p value
Sinus Venous Thrombosis	9 (19%)	7 (24%)	2 (11%)	0.45
Upper Extremity/Line-associated	17 (36%)	10 (35%)	7 (39%)	0.75
Lower Extremity	9 (19%)	5 (17%)	4 (22%)	0.71
Pulmonary Embolism	7 (15%)	3 (10%)	4 (22%)	0.40
Intracardiac	1 (2%)	1 (4%)	0	0.99
Other	4 (8.5%)	3 (10%)	1 (6%)	0.99

*
47 clots were diagnosed in 43 patients

Table V

Complications of 43 Patients with Asparaginase-Associated VTE

	All patients	Paediatrics	Adults
Total	43	27	16
Anticoagulation Complications			
Bruising	1 (2%)	0 (0%)	1 (6%)
Epistaxis	4 (9%)	2 (7%)	2 (13%)
Major Bleeding ^I	2 (5%)	0 (0%)	2 (13%)
VTE Complications			
Postphlebotic Syndrome	3 (7%)	0 (0%)	3 (19%)
Chronic Headaches	6 (14%)	4 (15%)	2 (13%)
Catheter Removal	9 (21%)	4 (15%)	4 (25%)
Restarted Asparaginase	33 (77%)	20 (74%)	13 (81%)
VTE Recurrence	11 (26%)	4 (15%)	7 (44%)
Deaths from VTE	0 (0%)	0 (0%)	0 (0%)

^IMajor bleeding: 1 intracranial hemorrhage, 1 compartment syndrome after bone marrow aspirate