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Venous thromboembolism prevention during asparaginase-based therapy for acute lymphoblastic leukemia

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ABSTRACT

Background Venous thromboembolism (VTE) is a recognized complication in patients treated with asparaginase-containing chemotherapy regimens; the optimal preventive strategy is unclear. We assessed the safety and efficacy of prophylaxis using low-dose low molecular weight heparin in adult patients with acute lymphoblastic leukemia in complete remission treated with an asparaginase-based post-remission chemotherapy regimen.

Methods As part of the intensification phase of the Dana-Farber Cancer Institute 91-01 regimen, asparaginase was administered weekly to 41 consecutive patients for 21–30 weeks; these patients also received prophylaxis with enoxaparin 40 mg daily (60 mg for patients ≥80 kg). Outcomes were assessed against outcomes in a comparable cohort of 99 patients who received the same chemotherapy regimen without anticoagulation prophylaxis.

Results The overall rate of symptomatic venous thrombosis was not significantly different in the prophylaxis and non-prophylaxis cohorts (18.92% and 21.74% respectively). Among patients receiving prophylaxis, VTE occurred in higher proportion in those who weighed at least 80 kg (42.86% vs. 4.35%, $p = 0.0070$). No major bleeding complications occurred in the prophylaxis group (minor bleeding: 8.1%).

Conclusions Prophylaxis with low-dose enoxaparin during the intensification phase was safe, but was not associated with a lower overall proportion of VTE.

Key Words Anticoagulants, asparaginase, leukemia, venous thromboembolism, prophylaxis

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INTRODUCTION

Venous thromboembolism (VTE) is a well-established complication in cancer patients[1–4], including those with hematologic malignancies[5,6]. Asparaginase is a key chemotherapy drug used in regimens for pediatric acute lymphoblastic leukaemia (ALL). Such regimens, which are associated with improved survival compared with older regimens[7], are now widely used in the treatment of children and young adults with ALL. Effective delivery of asparaginase, particularly during the post-remission intensification phase, appears to be crucial in achieving optimal outcomes in both children and adults[7,8]. Pediatric data from the Dana–Farber Cancer Institute (DFCI) showed that completion of 26 or more of the planned 30 weeks of asparaginase during the intensification phase was associated with a more favourable outcome[8].

Asparaginase is associated with an increased risk of VTE[9,10] that is largely related to inhibition of hepatic protein synthesis, leading to decreased plasma levels of antithrombin and proteins C and S[11,12]. In ALL, increased age has been identified as a risk factor for VTE, the incidence being 34% in adults compared with 5% in pediatric patients treated with asparaginase-containing regimens[13]. In another single-centre retrospective study, a 23% incidence of VTE was reported during the intensification phase of the pediatric-based DFCI 91-01 protocol in adults[8].

[a] These authors share senior authorship of the present work.

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A multicentre study using DFCI 91-01 in adults 18–60 years of age also reported a 23% incidence of thrombosis during the intensification phase and a 1% incidence during the induction phase[14]. Few data have been reported about the prevention of VTE in such patients. A study in pediatric ALL patients treated with an asparaginase-containing regimen demonstrated that the use of low-molecular weight heparin (LMWH) prophylaxis was associated with a low risk of VTE[15]; however, the control group in that study had only a 4% VTE rate. A prospective nonrandomized study in children with ALL, comparing antithrombin alone with antithrombin plus LMWH, found that prophylaxis with enoxaparin was associated with a lower proportion of VTE (12.7% vs. 0%, $p = 0.02$), without an increase in bleeding complications[16]. However, to the best of our knowledge, no studies using prophylaxis in adults have been reported to date, and hence evidence-based VTE prevention guidelines for that group of patients are lacking. The safety of anticoagulation prophylaxis in patients receiving such myelosuppressive chemotherapy has also not been established in adult patients.

Given the high proportion of VTE previously reported at our centre[8], we instituted routine anticoagulation prophylaxis with LMWH in all adults with ALL who received the asparaginase-containing intensification phase of the modified DFCI 91-01 protocol. We now report the VTE outcomes and safety of that approach, and we compare those results with a historical cohort that had received the same protocol without prophylaxis.

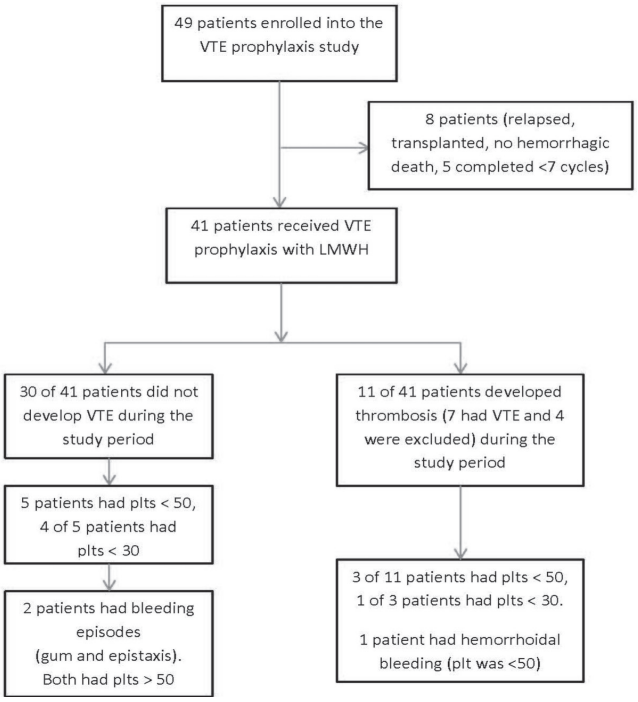

FIGURE 1 Patient enrolment schema: Patients who did and did not develop venous thromboembolism (VTE) during study period were compared. LMWH = low molecular weight heparin; plt(s) = platelet(s).

METHODS

This retrospective single-centre study at the Princess Margaret Cancer Centre (Toronto, ON), which is the primary regional referral centre for adult acute leukemia, identified patients in the leukemia database. Patient charts and hospital pharmacy records were reviewed to ensure data accuracy. Prior institutional ethics review board approval was obtained for this retrospective review.

Patients and Treatment

The study population included adult ALL patients in complete remission who received anticoagulation prophylaxis during the intensification phase of the modified DFCI 91-01 protocol between 2009 and 2012 (Figure 1). During that period, VTE prophylaxis was instituted as the standard of care. Details of the intensification phase of the regimen, including dose adjustments, have previously been described[8], and include intramuscular asparaginase 12,500 U/m^2 once weekly for 30 weeks (Table I). Patients 60 years of age and older received a modified version of the protocol with a 21-week intensification phase using intramuscular asparaginase 6000 U/m^2 once weekly as previously described[17] (Table I).

Patients who received at least 7 cycles (21 weeks) of the asparaginase-based intensification phase were included in the analysis. The VTE assessment included only patients who developed symptomatic deep-vein thrombosis (DVT) and pulmonary embolism (PE). Per the VTE standardized reporting suggested by Carrier *et al.*[18], catheter-related thrombosis and other type of thrombosis were excluded. Patients already on anticoagulation for prior VTE and patients who did not complete at least 7 cycles of intensification were also excluded from analysis unless early protocol discontinuation was the result of a VTE or major bleeding event. No patients with a baseline creatinine clearance of less than 30 mL/min were included. Patients who developed renal impairment during the study period were monitored closely, and their enoxaparin dose was either temporarily withheld or adjusted, as appropriate. *Escherichia coli*–derived asparaginase was used in all cases. Patients with *BCR-ABL1*–positive ALL were not included, because asparaginase was removed from their protocol during the fall of 2010; in addition, many of those patients were transplanted early.

Anticoagulation prophylaxis consisted of subcutaneous enoxaparin given once daily, at a dose of 40 mg for patients weighing less than 80 kg and 60 mg for those weighing 80 kg or more, beginning on day 1, cycle 1, of intensification and continuing until the completion of the entire 21- or 30-week intensification phase. The rationale for the dosing difference was derived from the observation that larger patients (weighing 80 kg or more) developed VTE while receiving the 40-mg dosing regimen. An amendment to a higher dose was proposed, and the team deliberated with concerns about potential bleeding risks and agreed to a 60-mg dose instead of an even higher dose. Patients receiving the 60-mg dose were closely monitored. The first dose of enoxaparin was administered in the clinic; subsequent doses were given by homecare nurses until patients were able to self-administer. Compliance was checked at each clinic

TABLE I Dana–Farber Cancer Institute protocol for adult acute lymphoblastic leukemia, intensification phase

Age group	Drug	Dose and route	Schedule
Age < 60 years (30 weeks, 21 days per cycle)			
	Dexamethasone	Oral, 9 mg/m^2	Twice daily, days 1–5
	Vincristine[a]	Intravenous, 2 mg	Day 1
	Doxorubicin	Intravenous, 30 mg/m^2	Day 1, cycles 1–7
	6-Mercaptopurine	Oral, 50 mg/m^2	Days 1–14
	Asparaginase	Intramuscular, 12,500 IU/m^2	Days 1, 8, and 15
	Methotrexate	Intravenous, 30 mg/ m^2	Days 2, 9, and 16; cycles 8–10
	Cytarabine–methotrexate–hydrocortisone	Intrathecal, 40 mg–12 mg–15 mg	Every 18 weeks
Age ≥ 60 years (21 weeks, 21 days per cycle)			
	Dexamethasone	Oral, 6 mg	Twice daily, days 1–5
	Vincristine[a]	Intravenous, 2 mg	Day 1
	Doxorubicin	Intravenous, 30 mg/m^2	Day 1
	6-Mercaptopurine	Oral, 50 mg/m^2	Days 1–14
	Asparaginase	Intramuscular, 6000 IU/m^2	Days 1, 8, and 15
	Cytarabine–methotrexate–hydrocortisone	Intrathecal, 40 mg–12 mg–15 mg	Every 18 weeks

[a] For patients with grade III or IV neuropathy, substitute intravenous vinblastine 10 mg.

visit, every 3 weeks. Platelet counts were monitored once weekly during the intensification phase. Enoxaparin was temporarily stopped if the platelet count fell below 30×10^9/L, if the patient experienced significant bleeding, or if renal function was severely impaired (creatinine clearance < 30 mL/min). The enoxaparin was reinstituted when platelets recovered, bleeding stopped, or renal function improved.

Results in the contemporary group were compared with results from a historical cohort of consecutive adult patients with ALL treated at the same institution who received at least 7 cycles of intensification using the same DFCI protocol during 2001–2009, before institution of VTE prophylaxis as the standard of care.

All suspected VTE events were confirmed with appropriate diagnostic testing. The VTE events were appropriately defined according to the described criteria and rationale[18]. Patients who developed VTE during the intensification phase were treated using therapeutic doses of LMWH. In most cases, asparaginase was held while the patient received full anticoagulation for 2 weeks, after which the chemotherapy was resumed. Many patients retained their central venous Hickman catheters during the intensification phase; the exact number could not be determined retrospectively.

Outcome Measures

Only confirmed DVT and PE were included in the analysis[18]. The primary endpoint of the study was the clinical efficacy of VTE prevention with the use of enoxaparin compared with no anticoagulation in a historical control group. The secondary endpoint was the safety of LMWH prophylaxis during the treatment period, as determined by bleeding events. Severity of bleeding was determined using the definitions set out by the International Society on Thrombosis and Haemostasis (ISTH)[19].

Statistical Methods

Descriptive statistics are used to summarize baseline patient demographics, disease characteristics, and laboratory data. Categorical variables such as sex, VTE proportions, and VTE sites are summarized with counts and percentages. Continuous variables such as age at diagnosis and weight are expressed as means ± standard deviation or medians with ranges. As appropriate, chi-square or Fisher exact tests were used to assess any association of the categorical variables with the proportions of VTE. Comparisons of cumulative VTE incidences were performed using the log-rank test. All p values were two-sided and, for the statistical analyses, $p < 0.05$ was considered to indicate a significantly different result. Data analyses were performed using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.).

RESULTS

Clinical Efficacy

Of 49 patients enrolled on enoxaparin prophylaxis during the intensification phase, 41 underwent at least 7 cycles and were eligible for analysis; the remaining patients received fewer than 7 cycles of intensification because of early relapse, allogeneic stem-cell transplantation, or non-hemorrhagic death. During treatment, no patient failed to start anticoagulation prophylaxis because of a pharmacologic contraindication, and no patient was lost to follow-up. No patient had to permanently discontinue prophylaxis.

The overall VTE rate was 7 of 37 in the prophylaxis cohort (18.92%) compared with 20 of 92 in the non-prophylaxis cohort (21.74%) [relative risk: 0.8815; 95% confidence interval (CI): 0.44 to 1.78; $p = 0.7218$]. In the prophylaxis cohort, the median number of treatment cycles completed was 10 cycles for patients less than 60 years of age, and 7 cycles for patients 60 years of age and older. The median duration of

LMWH use was 210 days in the younger group and 147 days in the older group. In the control group, the median number of treatment cycles completed was identical for both age groups. Although all patients eventually completed all cycles of intensification per the protocol, patients who developed VTE had temporarily stopped chemotherapy and started full-dose anticoagulation treatment for 2 weeks before resuming chemotherapy.

In the prophylaxis cohort, VTE events occurred at a median of cycle 3. In the control group, the median cycle was cycle 5. In a few patients, LMWH was temporarily withheld either because of medical procedures (for example, lumbar puncture with intrathecal chemotherapy administration) or a need for platelet count recovery. No patient developed thrombosis during those interventions. No patient received fewer than 7 cycles of chemotherapy because of either a VTE or a major hemorrhagic event.

The historical non-prophylaxis cohort did not significantly differ from the prophylaxis cohort with respect to median age, percentage of patients more than 60 years of age, weight, T- versus B-cell subtype, or ALL risk category (Table II). The mean enoxaparin dose administered in the prophylaxis group was 0.62 mg/kg (range: 0.39–1.05 mg/kg).

The analysis of symptomatic VTE excluded thrombosis other than DVT and PE from each of the cohorts. In the prophylaxis cohort ($n = 41$), 4 events were excluded (2 catheter-related and 2 sagittal sinus thromboses), and in non-prophylaxis cohort ($n = 99$), 7 events were excluded (5 catheter-related, 1 retinal vein, and 1 inferior vena cava thrombosis), leaving denominators of 37 in the prophylaxis group and 92 in the non-prophylaxis group. Table III shows the proportion of patients diagnosed with VTE in each group. The relative risk of experiencing a VTE while on prophylaxis was 0.8815 times that of experiencing a VTE while not on prophylaxis (95% CI: 0.44 to 1.78).

We observed no significant difference in the proportion of thrombotic events according to age, sex, or disease-risk status. The time to occurrence of thrombosis ranged from cycle 2 to cycle 10 and did not differ between the prophylaxis and historical cohorts (Figure 2). As shown in Table III, the overall proportion of thrombotic events was not significantly different between the prophylaxis and non-prophylaxis cohorts (18.92% and 21.74% respectively). Among patients receiving prophylaxis, the proportion of those experiencing thrombosis was higher in patients who weighed at least 80 kg than in those who weighed less than 80 kg ($p = 0.03$) despite the higher enoxaparin dose used in the former subgroup (Table IV). In the non-prophylaxis group, the proportion of those experiencing thrombosis was nonsignificantly different in patients weighing less than 80 kg (20.31%) and in those weighing 80 kg or more (25.00%). For patients whose weight was less than 80 kg, the relative risk of experiencing VTE while on prophylaxis was 0.2370 times the risk of experiencing VTE while not on prophylaxis (95% CI: 0.03 to 1.62). For patients whose weight was 80 kg or more, the relative risk of experiencing VTE while on prophylaxis was 1.6731 times that of experiencing VTE while not on prophylaxis (95% CI: 0.73 to 3.85). Figure 3 shows the sites of thrombosis in the prophylaxis group; some experienced thrombosis at more than 1 site (for example, DVT plus PE).

TABLE II Baseline patient characteristics

Characteristic	Received prophylaxis		*p* Value
	Yes	No	
Patients (*n*)	41	99	—
Median age (years)	40	37	NS
Age group [*n* (%)]			
<60 years	34 (83)	86 (87)	NS
≥60 years	7 (17)	13 (13)	
Sex (men:women)	30:11	63:36	NS
Phenotype [*n* (%)]			
Pre-B	28 (68)	74 (74)	NS
T	10 (24)	25 (26)	
Mixed	3 (8)	0	
WBCs at presentation (*n*)[a]			
High	11	12	NS
Low	30	78	
Cytogenetics or molecular (*n*)			
Normal	10	24	
MLL rearrangement	1	4	
Hyperdiploid	3	3	
Complex	5	11	
Other	10	20	
Not available	12	37	NS
Weight group [*n* (%)]			
<80 kg	26 (63)	67 (68)	NS
≥80 kg	15 (37)	32 (32)	

[a] Defined as more than 30×10^9/L (B-ALL) or more than 100×10^9/L (T-ALL).

WBCs = white blood cells; ALL = acute lymphoblastic leukemia.

TABLE III Proportion of venous thromboembolism (VTE) by site in the study groups

Site	Received prophylaxis [*n* (%)]		Overall
	Yes	No	
No VTE	30 (73.17)	72 (72.73)	102
Deep vein thrombosis (DVT)	4 (9.76)	16 (16.16)	20
Pulmonary embolism (PE)	1 (2.44)	3 (3.03)	4
PE+DVT	1 (2.44)	1 (1.01)	2
Central venous catheter (CVC)	2 (4.88)	5 (5.05)	7
CVC+PE (catheter-related)	1 (2.44)	0 (0)	1
Other	2 (4.88)	2 (2.02)	4
TOTAL	41	99	140

Safety

As defined by the ISTH[19], no major bleeding complications were observed in our prophylaxis population. Minor bleeding was documented in 3 of 41 patients (8.1%) at sites consisting of hemorrhoidal plexus veins, gingiva, and nose. Of 3 patients with minor bleeding, 2 had bleeds

associated with a platelet count exceeding 50×10^9/L. Those episodes occurred in the group of patients ($n = 30$) who did not developed VTE during the study. Within that group of 30 patients, 5 had platelet counts that dropped below 50×10^9/L, and 4 of those 5 patients had platelet counts that dropped below 30×10^9/L. In the latter 4 patients, LMWH was withheld for at least 1 week, but no patient experienced a breakthrough VTE event during that time. A drop in platelet level below 50×10^9/L occurred in 1 patient who experienced minor hemorrhoid bleeding and who also developed a VTE event during prophylaxis. Of 11 patients who developed VTE events during the study, 3 had a platelet level less than 50×10^9/L, and of those 3 patients, 1 had a platelet level below 30×10^9/L. Although no patients with a baseline creatinine clearance below 30 mL/min were included in the analysis, no patient receiving prophylaxis as the standard of care had a baseline renal function below that threshold. None of the patients experiencing VTE developed hypersensitivity reactions to asparaginase.

DISCUSSION

Thromboprophylaxis with LMWH has been recommended to prevent VTE in various subsets of cancer patients[20,21].

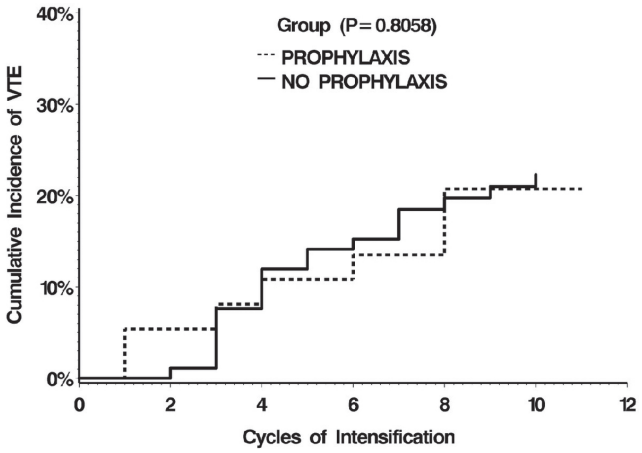

FIGURE 2 Cumulative incidence of venous thromboembolism (VTE) stratified by prophylaxis and no prophylaxis. The time to occurrence of VTE ranged from cycle 2 to cycle 10. The incidence of VTE increased over time with the increase in the number of cycles of asparaginase. The cumulative VTE incidence did not differ between the prophylaxis and the non-prophylaxis historical cohort by log-rank test ($p = 0.8058$).

The high proportion of VTE seen in patients receiving asparaginase-containing chemotherapy regimens for ALL has prompted some centres to institute routine anticoagulation prophylaxis for such patients. However, there is a paucity of data about the efficacy and safety of that approach, particularly in adults. The current retrospective analysis found that prophylaxis with low-dose LMWH can be safely administered to patients receiving post-remission intensification therapy in a modified DFCI 91-01 protocol. No major bleeding, as defined by the ISTH, occurred in our prophylaxis recipients. Because severe thrombocytopenia is uncommon during that treatment phase, it is unclear whether our observations can be extended to other more myelosuppressive regimens, or to the induction phase, in which severe thrombocytopenia is common.

However, the overall rate of symptomatic thrombosis in our analysis was not significantly different from the rate observed in the historical cohort that did not receive prophylaxis. Although the two cohorts were well matched with respect to baseline demographic factors and ALL risk criteria, we cannot exclude the possibility that unrecognized differences might have influenced the results. The use of high-dose corticosteroids could have contributed to the high rate of thrombosis in our cohorts, as previously described[22]. However, the incidences of thrombosis increased over time with the increase in the number of asparaginase cycles. In light of the VTE risk with corticosteroid and asparaginase exposure in both cohorts, the cumulative dose of each agent differed in terms of the total cycles of chemotherapy according to age, as previously described (7 cycles vs. 10 cycles). All patients who developed VTE in the prophylaxis cohort were 60 years of age or younger. Similarly, in the non-prophylaxis cohort, most patients who developed VTE fell into that age category. Only 2 of 20 patients experiencing VTE were more than 60 years of age. Their episodes could have been related to the additional doses of asparaginase and steroids within the 3 additional cycles of the intensification protocol. Lower-limb DVT in the non-prophylaxis cohort occurred in 16 of 99 patients (16.16%); in the prophylaxis cohort, it occurred in 4 of 41 patients (9.76%). The higher rate of thrombosis seen in patients receiving prophylaxis who weighed more than 80 kg seems to suggest that the dose of LMWH was insufficient and that perhaps a more intensive weight-based dosing nomogram, as described in other settings, would be more effective[23]. In our prophylaxis group, 6 of 7 patients who developed VTE weighed more than 80 kg and might have had additional risk factors leading to breakthrough VTE. Unfortunately, the sample size was too small to have demonstrated such an effect.

TABLE IV Overall venous thromboembolism (VTE) and weight distribution in the study groups

Variable	Received prophylaxis [*n* (%)]		RR	95% CI	*p* Value
	Yes	No			
Overall rate	7/37 (18.92)	20/92 (21.74)	0.8815	0.44 to 1.78	0.7218
Weight <80 kg	1/23 (4.35)	13/64 (20.31)	0.2370	0.03 to 1.62	0.1010
Weight ≥80 kg	6/14 (42.86)	7/28 (25.00)	1.6731	0.73 to 3.85	0.2980
p Value (<80 kg vs. ≥80 kg)	0.0070	0.6160			

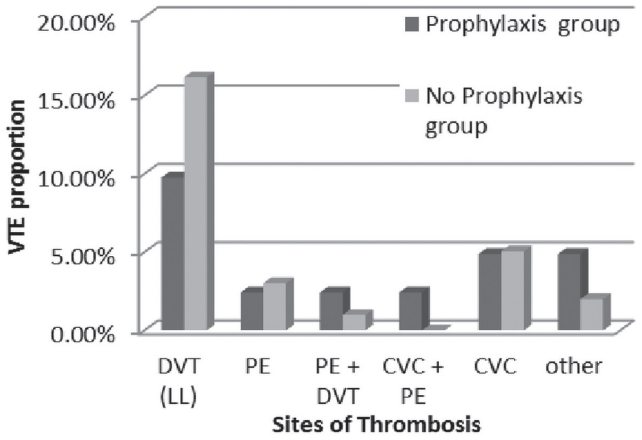

FIGURE 3 Sites of venous thromboembolism (VTE) in the groups receiving and not receiving prophylaxis with low molecular weight heparin. Overall VTE (DVT and PE) appeared to occur in lower proportion in the prophylaxis group. DVT = deep vein thrombosis; LL = lower limb; PE = pulmonary embolism; CVC = central venous catheter.

Based on the present work, we have now implemented a more intensive prophylactic regimen, targeting an enoxaparin dose of approximately 1 mg/kg daily, in large sample of patients receiving the modified DFCI 91-01 protocol. Without the safety data from the low-dose prophylaxis study, it would have been difficult for us to implement prophylaxis using 1 mg/kg dosing in this group of active chemotherapy recipients. The mean enoxaparin dose in the present study [0.62 mg/kg (range: 0.39–1.05 mg/kg)] reflects the dose amendment made (to 60 mg from 40 mg once daily) when we observed breakthrough VTE in larger patients (≥80 kg).

Other potential approaches to reduce the rate of VTE could include the routine use of mechanical compression stockings or the early removal of the central venous catheter, which can predispose to thrombosis[24]. However, the latter course of action would be unlikely to have influenced our results, because only 2 subclavian clots were documented in our prophylaxis cohort. Furthermore, mechanical compression stockings have not been shown to add prevention value. It is also possible that—given the severe depletion of antithrombin III induced by asparaginase—heparin and its derivatives might not be the most effective anticoagulant in this setting. Studies using newer anticoagulants as prophylaxis—for example, factor Xa inhibitors (apixaban, rivaroxaban, or edoxaban) or direct thrombin inhibitors (dabigatran, for instance)—would be warranted in these patients. However, the safety of those agents in such patients is unknown, and there are potential issues with the newer agents concerning drug interactions and difficulties in reversing bleeding. Antithrombin III concentrates have been used effectively in the induction setting[15]; however, its routine use in a prolonged intensification phase would be impractical.

In addition to the limitations already outlined, we did not perform serial venous Doppler ultrasongraphy testing in the study patients. It is therefore possible that subclinical VTE might have been missed. However, such instances would not have been clinically relevant. The fact that several VTEs were diagnosed within the first 2 cycles of intensification (Figure 2) indicates the possibility that some VTEs might actually have developed during the induction phase, when a single large dose of asparaginase is administered and patients are more likely to be confined to bed, given that they are in hospital during that phase. Our sample size was small, and it could be comparatively disadvantaged in relation to the historical patient cohort. To exclude that possibility, future studies aimed at demonstrating the benefit of prophylaxis strategies should incorporate baseline venous Doppler studies of the legs at the start of intensification. In addition, documentation of VTE during the induction phase would require earlier institution of prophylaxis, and the safety and efficacy of such an approach would have to be established. Although prophylaxis adherence by the patients was assessed during regular clinic visits, we do not have an actual account of the doses administered in our retrospective study. That having been said, we believe that the patients were informed and empowered to maintain high rates of administration.

CONCLUSIONS

The safety data in this cohort of patients were quite compelling, as demonstrated by the limited number of bleeding episodes that occurred with receipt of LMWH. Moreover the degree of severity was minor, as assessed by ISTH guidelines. Patients weighing more than 80 kg had higher rate of VTE despite prophylaxis with a higher LMWH dose.

Given high thrombosis rates and the challenges of dealing with thrombosis-related complications in patients receiving asparaginase, prospective randomized studies are needed to determine the optimal preventive strategies. Given the uncommon nature of ALL in adults, sample size and patient accrual should be optimized in a multicentre cooperative group approach. Retrospective data such as ours provide a basis for determining the most rational study designs.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: JTS has received honoraria as a speaker consultant from Leo Pharma, Merck Canada, Pfizer, and Amgen. JTS received study grants from Merck Canada and Amgen and from Sanofi in the form of compassionate supply of enoxaparin. The remaining authors declare that they have no conflicts.

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