Secondary Prevention of Venous Thromboembolic Events in Patients With Active Cancer: Enoxaparin Alone Versus Initial Enoxaparin Followed by Warfarin for a 180-Day Period

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Summary: This study evaluated enoxaparin alone versus initial enoxaparin followed by warfarin in secondary prevention of venous thromboembolic events in adults with active malignancy. Cancer patients (n = 122) with acute symptomatic venous thromboembolic events were randomly allocated to receive subcutaneous enoxaparin 1.0 mg/kg every 12 hours for 5 days, followed by 1.0 mg/kg daily (group 1a) or 1.5 mg/kg daily (group 1b) for 175 days, or subcutaneous enoxaparin 1.0 mg/kg every 12 hours for at least 5 days and until a stable international normalized ratio of 2 to 3 was achieved on oral warfarin begun on day 2 and continued to day 180 (group 2). There were no significant differences in major and minor bleeding rates between treatment groups. No bleeding events were intracranial or fatal. Enoxaparin treatment was feasible, generally well tolerated, and effective for a 180-day period in the secondary prevention of venous thromboembolic events in patients with active malignancy.
Key Words: Enoxaparin—Deep venous thrombosis—Malignancy

Venous thromboembolic events (VTEs), including deep venous thrombosis (DVT) and pulmonary embolism, warrant prompt initiation of antithrombotic therapy to prevent thrombus extension, embolization, and early as well as late recurrence. Challenges of VTE management in cancer patients compared with noncancer patients include greater heparin resistance due to excess circulating acute-phase proteins, increased recurrence and bleeding rates during standard-intensity oral warfarin therapy, variable nutrition status, greater difficulty maintaining an international normalized ratio (INR) of between 2 and 3 (43.3% time within range compared with 56.9% in noncancer patient controls), and limited venous access to support therapeutic monitoring.[1-3] Bleeding during anticoagulation is of particular concern in patients with disease-related and therapy-related thrombocytopenia and cancer that involves the central nervous system.

In the setting of acute VTE, the low-molecular-weight heparin (LMWH) enoxaparin has been shown to be equally effective and safe for initial anticoagulation compared with unfractionated heparin.[4,5] Enoxaparin has the advantage of less nonspecific protein binding, subcutaneous weight-based dosing without the need for monitoring in most cases, and less heparin-induced thrombocytopenia (HIT).[6,7] Subcutaneous, weight-based enoxaparin has also

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become a popular warfarin substitute in patients with VTE who have difficult to regulate INRs or have recurrent thrombosis despite an INR of between 2 and 3 ("warfarin failure"), as is often seen in cancer patients.

We performed this study to evaluate patient recruitment, safety, efficacy, and compliance for a 180-day period of enoxaparin alone versus initial enoxaparin followed by warfarin in the secondary prevention of VTE in adult patients with active malignancy. Baseline hemostatic profiling and assessment for inherited hypercoagulable states were performed to partially characterize the pathogenesis of thrombosis associated with cancer. Testing for heparin-associated antibodies was performed to evaluate the risk of HIT in enoxaparin-exposed cancer patients who are already prone to thrombocytopenia by virtue of their disease.

PATIENTS AND METHODS

This pilot feasibility study was conducted as a randomized, open-label, multidose, active comparator, parallel-design trial. Patients were randomized to receive 1 of 3 treatments. Group 1a received subcutaneous twice-daily enoxaparin (1.0 mg/kg) for 5 days, followed by once-daily enoxaparin (1.0 mg/kg) for 175 days; group 1b received subcutaneous twice-daily enoxaparin (1.0 mg/kg) for 5 days, followed by once-daily enoxaparin (1.5 mg/kg) for 175 days; and group 2 received subcutaneous twice-daily enoxaparin (1.0 mg/kg) for a minimum of 5 days and until achievement of a stable INR between 2 and 3 on oral warfarin begun on day 2 of enoxaparin and continued for a total of 180 days of anticoagulation. Patients were monitored for 7 months from the date of randomization.

The primary objectives of this trial were to evaluate the feasibility of recruiting the necessary number of cancer patients (300 evaluable patients) in a 12-month time frame and to evaluate the feasibility of compliance with long-term daily subcutaneous enoxaparin injections in active cancer patients with acute VTE. Compliance was defined as the percentage of enoxaparin or warfarin doses dispensed that were actually taken by the patient.

The secondary objectives included an evaluation of the safety of enoxaparin treatment alone (groups 1a and 1b) compared with enoxaparin followed by warfarin treatment (group 2) administered for 180 days to prevent secondary VTE in cancer patients, as determined by assessment of major and minor bleeding rates and serious adverse events (SAEs). A bleeding event was considered major if it resulted in death, a serious, life-threatening clinical event requiring hospitalization, transfusion of at least 2 units of packed red blood cells, a fall in hemoglobin of 2 grams or more that was attributable to the bleeding event, a retroperitoneal, intracranial, or intraocular hemorrhage; the need for surgery or decompression of a closed space; or an ecchymosis or hematoma greater than 10 cm in diameter. Another secondary objective was to evaluate the efficacy of VTE treatment with enoxaparin alone (groups 1a and 1b) compared with enoxaparin followed by warfarin treatment (group 2).

Efficacy was determined by assessment of objectively confirmed recurrent VTE involving a not previously involved venous segment and symptomatic VTE extension within the same venous segment as the index event during treatment. Baseline testing for acquired and inherited hypercoagulable states was performed on the first day of the study. Testing for the development of heparin-associated antibodies was performed in groups 1a and 1b at each monthly follow-up evaluation. The Hemostasis Research Laboratories of Loyola University Medical Center, Chicago, Illinois, performed all special coagulation testing.

To be eligible for enrollment in this study, patients had to be aged 18 years or older, weigh 120 kg or less, and have a functional capacity based on Karnofsky performance scale of 60 or more, or an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2[8] based on the most recent performance status before their acute VTE. Patients could be enrolled or randomized within 72 hours of VTE diagnosis and if LMWH or unfractionated heparin had already been initiated as a standard of care therapy. All index VTEs had to be objectively confirmed by appropriate imaging studies. Catheter-associated VTE were not eligible index thrombotic events.

Patients had to have active, residual malignancy determined by the presence of measurable disease, persistently elevated tumor markers, metastatic disease after tumor debulking, or histologically or cytologically confirmed cancer. At study entry, a patient could not be a candidate for curative intent surgery. Based on the investigators' judgment, all patients had to have an estimated length of survival that would allow for study completion. The study imposed no general or dietary restrictions.

Patients were excluded from enrollment if they had an anticipated need for thrombolytic therapy, embolectomy, or placement of a new caval filter,

TABLE 1. Baseline Demographic Characteristics and Index Venous Thromboembolism Diagnosis: Safety Sample

Characteristic	Enoxaparin 1.0 mg/kg (n = 31)	Enoxaparin 1.5 mg/kg (n = 36)	Warfarin (n = 34)	Total (N = 101)
Age				
Mean ± SD	62.7 ± 13.4	64.0 ± 10.7	64.1 ± 12.4	63.7 ± 12.0
Range	35-80	36-79	40-87	35-87
Age category (%)				
≤50 years	6 (19.4)	3 (8.3)	7 (20.6)	16 (15.8)
51-60 years	6 (19.4)	11 (30.6)	2 (5.9)	19 (18.8)
61-70 years	8 (25.8)	9 (25.0)	15 (44.1)	32 (31.7)
>70 years	11 (35.5)	13 (36.1)	10 (29.4)	34 (33.7)
Race (%)				
Caucasian	25 (80.6)	29 (80.6)	32 (94.1)	86 (85.1)
Black	5 (16.1)	4 (11.1)	2 (5.9)	11 (10.9)
Asian	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.0)
Hispanic	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.0)
Other	1 (3.2)	1 (2.8)	0 (0.0)	2 (2.0)
Index VTE (%)				
PE	12 (38.7)	17 (47.2)	15 (44.1)	44 (43.6)
DVT	24 (77.4)	29 (80.6)	31 (91.2)	84 (83.2)
PE and DVT	7 (22.6)	10 (27.8)	13 (38.2)	30 (29.7)

SD = standard deviation; VTE = venous thromboembolic event; PE = pulmonary embolism; DVT = deep venous thrombosis.

as were those whose active cancer was acute leukemia or a localized cutaneous malignancy. Patients with any contraindication to anticoagulation, including severe liver disease, known nonirradiated intracerebral metastases, deep organ biopsy within 2 weeks, and major surgery within 1 week were excluded. Patients with a baseline INR of 2 or more, known or suspected severe renal insufficiency (creatinine clearance of 30 mL/min or less), history of HIT, history of warfarin-associated skin necrosis, and baseline platelet count of less than 50,000/μL were not eligible.

Safety evaluations were performed on the safety population defined as all randomized patients who received at least 1 dose of study medication. The intent-to-treat population included all patients in the safety population who had at least 1 follow-up measurement. Descriptive statistics were used to summarize the incidence of major and minor hemorrhagic events and the incidence of recurrent VTE. Statistical analyses were performed using SAS 8.2 (SAS Institute, Cary, SC). All statistical tests performed used 2-sided hypothesis tests at the overall 5% level of significance.

RESULTS

In the period from January 26, 2001, to March 28, 2002, 102 patients from 27 sites were recruited. The appropriate institutional review board at each investigative site approved this study, and all patients signed an approved informed consent form. Each of the 3 treatment arms had approximately equal numbers of subjects: 32 in the enoxaparin 1.0 mg/kg group, 36 in the enoxaparin 1.5 mg/kg group, and 34 in the warfarin group. One subject in the 1.0 mg/kg enoxaparin group did not receive study drug. Of the 101 patients in the safety sample, 91 were included in the intent-to-treat analysis. Nine patients (5 in the 1.0 mg/kg enoxaparin group and 4 in the 1.5 mg/kg enoxaparin group) did not meet full entry criteria and were enrolled after sponsor approval.

Table 1 summarizes the baseline demographic characteristics and index VTE diagnosis of the safety population. Most patients in the 1.5 mg/kg enoxaparin group were female (63.9%) and aged 51 years or older (58.3%). In contrast, the 1.0 mg/kg enoxaparin group was 51.6% female and 41.9% were aged 51 years or older. The warfarin group was 47.1% female and younger than those in the enoxaparin groups. Most patients in the 3 treatment arms were diagnosed with DVT, and more patients in the warfarin group had both DVT and pulmonary embolism. Overall, 8.7% of patients had a history of VTE before the study index event. None of these differences were statistically significant.

Of the 91 patients in the intent-to-treat population, 49 (53.8%) completed 180 days of study medication. The primary reasons for discontinuation from

TABLE 2. Reasons for Patient Withdrawal or Termination

Withdrawal Reasons	Enoxaparin 1.0 mg/kg, n = 32 (%)	Enoxaparin 1.5 mg/kg, n = 36 (%)	Warfarin, n = 34 (%)	Total, N = 101 (%)
Adverse event	1 (3.2)	5 (13.9)	1 (2.9)	7 (6.9)
Progressive disease	2 (6.5)	3 (8.3)	6 (17.6)	11 (10.9)
Study end point	4 (12.9)	2 (5.6)	1 (2.9)	7 (6.9)
Nonpermitted therapy	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.0)
Major protocol violation	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	3 (9.7)	2 (5.6)	2 (5.9)	7 (6.9)
Death	2 (6.5)	7 (19.4)	3 (8.8)	12 (11.9)
Malignancy	2 (6.5)	6 (16.7)	2 (5.9)	10 (9.9)
Fatal VTE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (2.8)	1 (2.9)	2 (2.0)
Other	0 (0.0)	2 (5.6)	4 (11.8)	6 (5.9)

VTE = venous thromboembolic event.

TABLE 3. Cancer Stage at Study Entry: Safety Sample

Cancer Stage	Enoxaparin 1.0 mg/kg, n = 31 (%)	Enoxaparin 1.5 mg/kg, n = 36 (%)	Warfarin, n = 34 (%)	Total, N = 101 (%)
I	2 (6.5)	0 (0)	2 (5.9)	4 (4.0)
II	2 (6.5)	4 (11.1)	1 (2.9)	7 (6.9)
III	7 (22.6)	8 (22.2)	9 (26.5)	24 (23.8)
IV	17 (54.8)	24 (66.7)	18 (52.9)	59 (58.4)
Unknown	3 (9.7)	0 (0)	4 (11.8)	7 (6.9)

the study differed among the treatment groups (Table 2). The discontinuation rate (58.3%) was highest in the enoxaparin group receiving 1.5 mg/kg, with the most common reasons being death (19.4%) and adverse events (13.9%). The lowest discontinuation rate (41.9%) was in the enoxaparin group receiving 1.0 mg/kg. The primary reason (12.9%) for discontinuation in this group was reaching the study end point (recurrent VTE or major hemorrhage).

Table 3 summarizes the cancer stage at study entry for the safety population. More subjects in the enoxaparin group receiving 1.5 mg/kg presented with stage IV cancer at the start of the study (66.7%) than in the other groups (54.8% and 52.9% for the 1.0 mg/kg and warfarin groups, respectively). It should be noted that there was a sizeable percentage of subjects with "unknown" cancer stage in the 1.0-mg/kg enoxaparin (9.7%) and the warfarin (11.8%) groups. More subjects in the 1.5-mg/kg enoxaparin group had also been treated with radiation therapy (38.9%) and chemotherapy (58.3%) than those in the 1.0-mg/kg enoxaparin (32.4% and 55.9%, respectively) and the warfarin groups (32.3% for both radiation and chemotherapy).

Compliance data were available for 98 of 101 treated subjects. The overall compliance rate in the 3 treatment groups averaged 95% throughout the study. Mean overall treatment compliance was slightly lower in the warfarin group (90.1%) than in the 1.0-mg/kg and 1.5-mg/kg enoxaparin groups (97.9% and 97.0%, respectively). Across all visits, 92 patients (91.1%) took 81% to 100% of their study drug. Six subjects (5.9%) took less than 81% of the dispensed drug. Compliance was poorest with warfarin (50% to 100% compliance) and best in the 1.0-mg/kg enoxaparin group (82% to 100% compliance).

Few patients experienced objectively confirmed symptomatic extension of their index VTE or true recurrent VTE (Table 4). More intent-to-treat patients in the warfarin treatment arm experienced VTE extension or recurrence than in either of the enoxaparin treatment arms. Three patients (10.0%) in the warfarin group, but only 2 patients in each of the enoxaparin groups (6.9% of 1.0 mg/kg group and 6.3% of 1.5 mg/kg group), experienced

TABLE 4. Analysis of Venous Thromboembolic Event Recurrence and Symptomatic Extension: Intent-to-Treat Sample

VTE Event	Enoxaparin 1.0 mg/kg, $n = 29$ (%)	Enoxaparin 1.5 mg/kg, $n = 32$ (%)	Warfarin, $n = 30$ (%)	Total, $N = 91$ (%)
Symptomatic extension of index VTE[a]	1 (3.4)	1 (3.1)	1 (3.3)	3 (3.3)
Recurrent VTE[b]	1 (3.4)	1 (3.1)	2 (6.7)	4 (4.4)
All VTE	2 (6.9)	2 (6.3)	3 (10.0)	7 (7.7)

VTE = venous thromboembolic event.
a. Extension of the index thrombosis within the same venous segments that were originally involved.
b. Detection of new thrombosis within a venous segment not previously involved.

TABLE 5. Summary of Adverse Events

Adverse Event	Enoxaparin 1.0 mg/kg, $n = 31$ (%)	Enoxaparin 1.5 mg/kg, $n = 36$ (%)	Warfarin, $n = 34$ (%)	Total, $N = 101$ (%)
Nonserious	27 (87.1)	32 (88.9)	29 (85.3)	88 (87.1)
Treatment-related, nonserious	3 (9.7)	6 (16.7)	8 (23.5)	17 (16.8)
Discontinued due to nonserious AE	1 (3.2)	0 (0.0)	2 (5.9)	3 (3.0)
SAE	16 (51.6)	23 (63.9)	17 (50.0)	56 (55.4)
Minor hemorrhage event	19 (61.3)	20 (55.6)	17 (50.0)	56 (55.4)
Major hemorrhage event	2 (6.5)	4 (11.1)	1 (2.9)	7 (6.9)
Died	7 (22.6)	15 (41.7)	11 (32.4)	33 (32.7)

AE = adverse event; treatment-related = probably or possibly related to the study drug, in the opinion of the investigator; SAE = serious adverse event.

VTE during anticoagulant treatment. Overall, 3.3% of study subjects experienced a symptomatic VTE extension and 4.4% experienced a new VTE for a total thrombosis event rate of 7.7%. No patient was diagnosed with a new pulmonary embolism during the study. Two patients not in the intent-to-treat sample, 1 in each of the enoxaparin groups, experienced recurrent DVT.

Because VTE developed in only a small number of patients in the study, no trends or significance could be observed. There was no effect of age, gender, race, clinical cancer stage, duration of cancer diagnosis, or type of index VTE on the probability that VTE would develop during the 6-month treatment period. Subjects with an ECOG performance status of 2, on the other hand, had a significantly increased risk of experiencing a VTE during the study than did subjects with a score of 0 or 1 (hazard ratio, 7.253; 95% confidence interval, 1.580 to 33.296; $P = .011$ from proportional hazards model).

Table 5 summarizes adverse events for the safety study population. Overall, 87.1% of patients experienced at least 1 nonserious adverse event during the study, and the number of events was evenly distributed among the 3 treatment groups. Approximately half of all study patients experienced at least 1 SAE during the study. The 1.0-mg/kg enoxaparin and the warfarin groups had similar SAE rates (51.6% and 50.0%, respectively), and the 1.5-mg/kg enoxaparin group had the highest incidence of SAEs (63.9% had at least 1 SAE). More cardiovascular SAEs occurred in the enoxaparin groups than in the warfarin group (6 and 9 versus 0), but the distribution of events in other body systems was nearly even across groups. Only 3 subjects in the study had SAEs that were considered to be "possibly" or "probably" related to the study drug: 2 in the warfarin group and 1 in the 1.0-mg/kg enoxaparin group.

Overall, 58 patients experienced at least 1 hemorrhagic event (major or minor) during the study. Seven patients experienced at least 1 major hemorrhagic event: 1 in the warfarin group, 2 in the 1.0-mg/kg enoxaparin group, and 4 in the 1.5-mg/kg enoxaparin group. All major hemorrhagic events were considered SAEs but were analyzed separately from other adverse events. The incidence and types of adverse events and hemorrhagic events observed with enoxaparin alone versus enoxaparin followed by warfarin were similar to those described in the package inserts and the investigator's brochure.

Of the 33 deaths during the 7-month observation period, 29 (88%) were attributable to progression of underlying malignancy. Of the remaining 4 subjects,

TABLE 6. Molecular Coagulation Studies

Laboratory Test	ONCENOX Subjects, n (%)
Factor V Leiden	
Normal	66 (92)
Heterozygous	6 (8)
Homozygous	0 (0)
Prothrombin G20210A	
Normal	71 (99)
Heterozygous	1 (1)
Homozygous	0 (0)
MTHFR C677T	
Normal	42 (58)
Heterozygous	24 (33)
Homozygous	6 (8)

MTHFR = 5,10-methylene tetrahydrofolate reductase.

1 each died of presumed pulmonary embolism (1.0-mg/kg enoxaparin group), VTE (1.0-mg/kg enoxaparin group), cardiac arrest (warfarin group), and heart failure (1.5-mg/kg enoxaparin group). Only 12 patients were discontinued from the study due to death (Table 2). The remainder of the patients who died during the 7-month observation period did so either after study discontinuation for another reason or after completion of the 180-day period of study medication.

There were no adverse trends in platelet count during the study. The mean and median values for platelet count were within the normal limits for all 3 groups at all study visits, including at baseline. Thrombocytopenia was reported in 7 patients: 5 in the warfarin group and 1 in each of the enoxaparin groups; however, a causal relationship to study medication was described for only 1 subject in the warfarin group.

Mean antifactor Xa activity levels were between 0.44 and 0.73 U/mL over the treatment period in the 1.0-mg/kg enoxaparin group and between 0.59 and 1.04 U/mL in the 1.5-mg/kg enoxaparin group. Overall, 25 samples had antifactor Xa activity levels of more than 2.00 U/mL. Most samples had antifactor Xa activity levels between 0.5 and 1.5 U/mL. Table 6 summarizes the results of molecular coagulation studies performed in the 72 study patients who provided informed consent for such testing. Factor V Leiden, prothrombin G20210A, and homozgous MTHFR C677T prevalence rates were 8%, 1%, and 8% respectively.

Table 7 summarizes the results of baseline coagulation studies. In addition, 74 patients underwent antigenic and functional tissue factor pathway inhibitor (TFPI) testing. Antigenic TFPI levels in 27% of tested patients were less than 70 ng/mL. As determined by functional TFPI testing, only 8% of patients had decreased levels. Anticardiolipin antibody testing showed that 7% had elevated titers of immunoglobulin (Ig)G anticardiolipin antibody, and 3% had elevated titers of IgM anticardiolipin antibody. Of 514 samples tested for anti-heparin-platelet factor 4 antibodies by enzyme-linked immunosorbent assay (ELISA), 60 samples from 31 different patients were positive. The titer varied from slightly positive (OD >0.40) to strongly positive (OD >1.00, 10 samples). Seven positive samples were baseline samples. When these 60 samples were tested by ^{14}C serotonin release assay, none were positive.

DISCUSSION

This clinical trial was designed as a 3-arm, pilot feasibility study to evaluate patient recruitment, compliance, safety, and efficacy for a 180-day period of treatment with enoxaparin alone versus enoxaparin followed by warfarin in the secondary prevention of VTE in patients with active malignancy. The objective to recruit the necessary number of patients within a 12-month time frame was not met; however, compliance, safety, and efficacy results were available for 102 enrolled patients.

The overall compliance rate in the 3 treatment groups was high, averaging 95% throughout the 6-month treatment period. Overall, average treatment compliance was slightly higher with enoxaparin alone (97.9% for 1.0-mg/kg and 97.0% for 1.5-mg/kg enoxaparin) than with warfarin (90.1%). This indicates that long-term subcutaneous administration of enoxaparin was generally well tolerated by patients. The need for daily subcutaneous injection was not an obvious deterrent to study participation or completion. The antifactor Xa activity levels observed in most patients treated with both doses of enoxaparin were within a range believed to be the desired target range for VTE treatment.

The incidence of recurrent VTE in the intent-to-treat population was numerically lower with enoxaparin therapy than with initial enoxaparin followed by oral warfarin. No numeric difference in the recurrent VTE rate was observed for the 2 studied once-daily enoxaparin dosages. Although statistical significance was not reached, the cumulative probability of being VTE-free at 6 months was numerically higher for enoxaparin alone than for enoxaparin followed by warfarin therapy. Standard of care included twice-daily subcutaneous administration of enoxaparin at 1.0 mg/kg for a minimum of 5 days, with warfarin therapy started within 48 hours of enoxaparin initiation

TABLE 7. Baseline Coagulation Studies

Laboratory Test[a]	Normal Controls	ONCENOX Subjects (range)	% Abnormal
APC-ratio			
First generation	> 2.0	2.2 ± 0.3 (1.3-2.7)	13
Second generation	> 2.0	2.6 ± 0.2 (1.8-3.2)	1
Antithrombin activity (%)	95.0 ± 9.5	104.4 ± 21.1 (47-154)	6
Protein C activity (%)	96.0 ± 8.9	82.5 ± 41.4 (4-200)	36
Protein S activity (%)	95.0 ± 8.3	69.3 ± 33.1 (18-172)	56
vWF antigen (%)	135.0 ± 23.8	224.0 ± 83.0 (75.4-556.7)	71
Factor VIII activity (%)	94.0 ± 7.8	111.0 ± 42.8 (1.0->200)	17
dRVVT	33.7 ± 8.6	58.2 ± 15.6 (23.9-142.4)	36
PAI-1 antigen (ng/mL)	32.1 ± 9.6	44.8 ± 19.6 (3.4-93.5)	34
TAFI activity (%)	90.0 ± 4.7	93.9 ± 15.9 (44.2-139.8)	24
TFPI antigen (ng/mL)	68 ± 13.7	74.0 ± 6.1 (62.5-92.5)	27

APC = activated protein C; vWF = von Willebrand factor; dRVVT = dilute Russell's viper venom time; PAI-1 = plasminogen activator inhibitor-1; TAFI = thrombin activatable fibrinolysis inhibitor.
a. Data presented as mean ± standard deviation (range).

with a target INR of 2.5 for 2 consecutive days (range, 2.0 to 3.0).[4] This was in accordance with recommendations by the Sixth American College of Chest Physician's Consensus Conference on Antithrombotic Therapy for the treatment of VTE.[9] The observed trend toward greater secondary VTE prevention with long-term enoxaparin compared with warfarin is in line with similar observations with enoxaparin and other LMWHs.[10-12]

Overall, the incidence, type, and intensity of adverse events observed with enoxaparin administered alone for 6 months in the current study were no more extensive than those described for the standard therapy of enoxaparin followed by warfarin. The higher rate of study discontinuation due to death in the 1.5-mg/kg enoxaparin group may reflect the greater number of patients with stage IV cancer and greater number of patients receiving chemotherapy or radiation therapy in this arm of the study. There were no unexpected adverse events or other clinically significant safety findings that negated the use of long-term enoxaparin therapy as an alternative to oral warfarin.

The prevalence rates for factor V Leiden heterozygosity, prothrombin gene G20210A heterozygosity, and homozygous MTHFR C677T did not differ significantly from rates reported for normal populations and are actually numerically less than rates reported for patients with idiopathic VTE.[13] Common molecular defects associated with hypercoagulability in general were clearly not the primary determinant of thrombosis in our cancer population. The baseline laboratory characterization reflects the complex and variable nature of the hypercoagulability of malignancy. Acquired activated protein C resistance based on testing of samples that have not been prediluted with factor V-deficient plasma (first generation) has been described in association with several tumor histologies.[14] Combinations of decreased levels of natural anticoagulants (eg, protein C, protein S, and TFPI), increased levels of procoagulant proteins (eg, factor VIII and von Willebrand factor), lupus anticoagulant activity, and increased levels of fibrinolytic inhibitors (eg, plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor) surely contributed to the original development of thrombosis in this population. Nonetheless, the likely ongoing hypercoagulability was adequately neutralized by once-daily enoxaparin at 1.0 mg/kg and 1.5 mg/kg as reflected by low VTE recurrence rates.

Ongoing and intermittent thrombocytopenia is often seen in patients with cancer involving the bone marrow and in those receiving cycles of cytotoxic therapy. The development of thrombocytopenia during daily LMWH therapy may raise reasonable concerns about HIT. For this reason, we evaluated patients for the development of heparin-associated antibodies. The detection of such antibodies in 31 enoxaparin-treated patients was not unexpected, because LMWH therapy may result in the generation of these antibodies. However, none of the detected antibodies were functional as determined by serotonin release assay. It seems prudent to recommend against making the diagnosis of HIT in active cancer patients receiving long-term enoxaparin solely from the detection of heparin-associated antibodies by ELISA.

CONCLUSION

This study demonstrated that treatment with enoxaparin was feasible, generally well tolerated, and effective for a 180-day period in the secondary prevention of VTE in patients with active cancer.

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APPENDIX 1. ONCENOX INVESTIGATORS

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