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Recurrence of venous thromboembolism in patients with cancer treated with warfarin

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Abstract

Venous thromboembolism (VTE) is a common complication in patients with cancer. Previous randomized studies have demonstrated that rates of recurrent VTE are lower in patients treated with low-molecular-weight heparin compared to warfarin. We performed a retrospective analysis of 236 patients with cancer managed by a dedicated oncology anticoagulation management service to compare "real-world" rates of recurrent VTE and bleeding in patients treated with warfarin versus parenteral anticoagulants. Initial anticoagulant regimen included a parenteral agent with transition to warfarin in 132 (55.9%) patients, enoxaparin in 53 (22.5%), dalteparin in 37 (15.7%), and fondaparinux in 14 (5.9%). Taking into account the competing risk of death, cumulative incidence of VTE recurrence at 6 months was 4.0% with warfarin, 10.3% with enoxaparin, 3.0% with dalteparin, and 7.7% with fondaparinux ($P = .004$). Bleeding complications occurred in 10.6% of patients on warfarin, 17.0% on enoxaprin, 27.0% on dalteparin, and 14.3% on fondaparinux ($P = .089$). In a dedicated anticoagulation clinic, specific for patients with cancer, warfarin may be an acceptable treatment for first thrombotic events in patients with cancer.

Keywords

anticoagulants; venous thromboembolism; hypercoagulability

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INTRODUCTION

The elevated risk of thrombosis in the setting of malignancy has been described for almost 200 years.[1] Approximately 20% to 30% of all first venous thromboembolic events (VTE) are related to malignancy, and cancer patients have a relative risk of venous thromboembolism between 4- to 7-fold higher than patients without cancer.[2,3] Rates of thromboses in large retrospective studies have been found to be as high as 8% to 12% in some solid tumors types.[4,5] Thromboses are more likely in patients with solid tumor having advanced malignancies, specific sites of cancer such as pancreatic, gastric, brain, and gynecologic, and in patients receiving chemotherapy.[6] Patients with hematologic malignancies area also at very high risk of thrombosis, with rates between 2% and 10% to 20% for many leukemias, lymphomas, and multiple myelomas.[7]

Thrombotic events affect morbidity, quality of life and cost of care, and also adversely affect patient mortality.[8,9] Treatment of VTE in the patients with cancer is complicated, as the risk of both recurrent thromboembolism and major bleeding is higher than in patients without cancer.[10] Patients with malignancy who develop thrombotic events are treated with systemic anticoagulation unless they have an absolute contraindication to anticoagulant therapy. Options for anticoagulation include oral vitamin K antagonists (after bridging with a parenteral agent), subcutaneous low-molecular-weight heparins (LMWHs), such as enoxaparin and dalteparin, and the synthetic pentasaccharide fondaparinux. The largest randomized trial of VTE treatment in patients with active cancer, the CLOT trial, found that dalteparin had greater efficacy than warfarin in preventing recurrent venous thromboembolism.[11] The LMWHs are currently recommended for initial treatment of malignancy-associated venous thromboembolism.

Few studies have evaluated the incidence of recurrent thromboses in ambulatory oncology clinics outside the setting of clinical trials. While LMWH is preferred, many patients are not able to be treated with LMWH for a variety of reasons including drug cost and intolerance of or inability to perform injections. Our center has a dedicated anticoagulation management service (AMS) that provides support for clinicians managing patients with cancer, having venous thromboembolism treated with all types of anticoagulants including both warfarin and LMWH.[12] We analyzed the rate of recurrent thrombosis in patients with malignancy cared for in this dedicated AMS.

PATIENTS/METHODS

Patient Identification and Eligibility

Following institutional review board approval, we identified patients with active malignancy and a diagnosis of venous thromboembolism managed by the AMS at the Dana-Farber Cancer Institute between January 1, 2008 and January 1, 2012. This patient population reflected patients managed by the AMS since initiation of anticoagulation therapy as well as patients for whom anticoagulation had been started by another provider and were later referred to the AMS. Inclusion criteria included patients 18 years or older, active malignancy - defined as cancer diagnosed or treated within 1 year of the diagnosis of venous

thromboembolism - and active anticoagulation - defined as use of an oral or parenteral anticoagulant for at least 1 month after the initial thrombosis.

Data Collection

Chart reviews were performed. Collected patient characteristics included age, gender, type of malignancy, and transplantation status in patients with hematologic malignancy. Information regarding VTE diagnosis included date, method of detection, location, initial anticoagulant regimen, and laboratory values at the time of VTE diagnosis including international normalized ratio (INR), partial thromboplastin time, platelet count, creatinine, alanine aminotransferase, and aspartate aminotransferase. The date and location of recurrent thrombosis, bleeding events, laboratory values at the time of these events, and patient outcomes including date and cause of death or last known follow-up were recorded. A bleeding event was defined as a composite result of major and clinically relevant nonmajor bleeds. Major bleeding was defined as overt bleeding that led to transfusion of red cells, occurred in a critical site, or contributed to death. Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for hospitalization, medical intervention, or interruption or discontinuation of anticoagulation.

Statistical Analysis

The primary aim was to compare the rate of first recurrent venous thromboembolic event in patients with cancer treated with warfarin versus a parenteral agent. The cumulative incidence rate of recurrent VTE was assessed by a competing risk analysis. Time to first recurrent VTE during the first anticoagulant regimen was measured from the time of diagnosis of the first clot to the first subsequent VTE, death, or termination of the first anticoagulant regimen, whichever occurred first. Death before recurrent VTE while on the first anticoagulant agent was considered as a competing risk event. Patients alive and without a recurrent VTE at the end of the first anticoagulant regimen were censored at the time anticoagulation was discontinued. Reasons for stopping the first anticoagulant include recurrent VTE, death, bleeding event, or were unknown based on information available. Differences in the incidence rate of recurrent VTE on different anticoagulant agents were evaluated by the Gray test, and the Fine and Gray regression model was used to assess the impact of the first anticoagulant regimen on the time to first recurrent VTE. Other covariates were similarly assessed. The number and proportion of patients with a recurrent VTE while on first anticoagulant is also provided along with the corresponding incidence rate calculated per person-time.

Overall survival (OS), defined as time from diagnosis of the first VTE to date of death from any cause, was estimated using the method of Kaplan and Meier and the log-rank test was used to compare OS between groups. Patients alive at the end of the follow-up period were censored at date of last known contact. Univariate logistic regression modeling was used to assess the impact of the first anticoagulant regimen on the probability of a bleeding episode on that regimen. Other covariates were also assessed using univariate logistic regressions.

Patient characteristics were summarized using proportions and ranges for categorical end points and medians for continuous end points. Fisher exact test and the Kruskal-Wallis test were used to compare categorical and continuous variables among groups, respectively. Statistical significance was defined as a P value <.05. Statistical analyses were performed using SAS statistical software (version 9.3, SAS institute) and the *cmprsk* package of R.

RESULTS

Baseline Characteristics

A total of 239 patients met the inclusion criteria. Three patients whose initial anticoagulant agent was either unknown (1 patient) or none (2 patients) after the first VTE were excluded from the analyses; data from 236 patients was included. The baseline characteristics of these patients are shown in Table 1. The median age was 61.7 years (range 19.5–88.9) and 100 (42.4%) patients were male. Of the patients, 169 (71.6%) had solid malignancies and 67 (28.4%) had hematologic malignancies. In patients with solid malignancies, breast (30 patients, 17.8%), colorectal (24 patients, 14.3%), and sarcoma (17 patients, 10.1%) were the most common. Ninety-eight (58%) patients with solid malignancy had metastatic disease. In patients with hematologic malignancies, non-Hodgkin lymphoma and multiple myeloma (22 patients, 32.8% for each type) were the most common. Of the patients with hematologic malignancy, 32 (47.8%) underwent hematopoietic stem cell transplantation either before study entry or during the time they were included in the study.

Venous Thromboembolism Type and Initial Management

In all, 122 (51.7%) patients had deep venous thrombosis (DVT), 69 (29.2%) had pulmonary embolism (PE), 22 (9.3%) had both DVT and PE, and 23 (9.7%) had thrombus in other locations including the portal vein, gonadal vein, intracranial vein, and intracardiac thrombosis. Initial anticoagulant agents included warfarin in 132 (55.9%) patients, enoxaparin in 53 (22.5%), dalteparin in 37 (15.7%), and fondaparinux in 14 (5.9%). The distribution of patient characteristics by type of first anticoagulation is shown in Table 2. Age at first clot, patient gender, malignancy type, stage of solid malignancy (localized versus metastatic), transplantation status (for hematologic malignancies), initial clot location, and whether a patient was on chemotherapy at the time of the first VTE did not differ significantly between different anticoagulation regimens. The time in therapeutic range (TTR) at our center for patients on warfarin was 59.5% during the study time period.

Recurrent Venous Thromboembolism while on First Anticoagulant Regimen

Taking into account the competing risk of death, cumulative incidence of VTE recurrence while on first anticoagulant at 6 months was 4.0% on warfarin, 10.3% on enoxaparin, 3.0% on dalteparin, and 7.7% on fondaparinux (Gray test $P = .004$). This is shown in Table 3 and Figure 1. Patients on enoxaparin were significantly more likely to develop recurrent VTE than those on warfarin (hazard ratio [HR] 4.65, 90% confidence interval [CI] 1.98–10.96, P value .003). The risk of recurrent VTE did not differ significantly between dalteparin and warfarin (HR 0.562, 90% CI 0.096–3.290) or fondaparinux and warfarin (HR 1.23, 90% CI 0.206–7.360). Wald test showed a significant difference in recurrent VTE by regimen when all 4 regimens were compared ($P = .013$), likely driven by the higher rate of recurrence in

patients on enoxaparin. Age, gender, malignancy type, transplantation status, or initial clot location did not significantly impact the risk of recurrence.

Bleeding Events while on First Anticoagulant Regimen

Of 132 patients, 14 (10.6%) developed bleeding events while on warfarin, compared to 9 (17.0%) of 53 patients on enoxaparin, 10 (27.0%) of 37 patients on dalteparin, and 2 (14.3%) of 14 patients on fondaparinux. There was no significant difference in the overall risk of bleeding among the regimens (Wald's test *P* value .108). These results as well as individual regimen comparisons are presented in Table 4.

Patient Outcomes

Median follow-up time for all patients was 43.3 months. Overall survival by anticoagulation type did not differ significantly between the regimens (log-rank P value .1041) and is shown in supplemental Figure 2. For warfarin, median OS was not reached, for enoxaparin it was 26.5 months, for dalteparin 34.5 months, and for fondaparinux 31.8 months. At 12 months, 80.2% of the patients initially treated with warfarin remained alive, compared to 71.7% of patients treated with enoxaparin, 80.8%with dalteparin, and 70.4%with fondaparinux. The most common cause of death in all patients was progressive malignancy. There were no fatalities related to bleeding.

DISCUSSION/CONCLUSIONS

We reviewed the rate of recurrent VTE in patients with malignancy referred to an AMS dedicated to patient with cancer at our institution. Patients treated with warfarin had a low rate of VTE recurrence of 5.3%, which compared favorably to 10.6% in patients treated with parenteral agents, with similar or even lower rates of bleeding. These results differ from those reported in several randomized controlled trials of warfarin versus a parenteral agent in patients with cancer including the largest study, the CLOT trial, in which there was a 17% recurrence rate for patients treated with warfarin compared to 9% in the dalteparin group at 6 months.[11,13–15] Reanalysis of data from the CLOT trial, however, using competing risk techniques and Gray test found that the original Kaplan-Meier method overestimated risk of recurrent VTE in both treatment groups by about 30%. Those treated with LMWH still had a significantly lower risk of recurrent clot than those treated with a vitamin K antagonist, but the magnitude of effect was not as large.[16,17]

Our patient population differs in many ways from those enrolled in randomized trials of warfarin versus an LMWH for treatment of first VTE in patients with cancer. Both referral bias and selection bias are inherent characteristics of this population which cannot adequately be controlled for. The majority of patients were referred to our AMS for warfarin initiation and management either because their primary oncologist felt that warfarin was an acceptable anticoagulant or because of inability to use parenteral agents for reasons such as cost or intolerance of injections. The AMS staff assisted in obtaining LMWH at reduced cost if possible—especially for those patients receiving chemotherapy regimens that significantly interfered with warfarin metabolism—but were not often successful. Some patients treated with a parenteral agent may have been referred to the AMS for the close monitoring the

service provided, as they were considered challenging due to perceived high risk of bleeding or recurrent thrombosis. These factors, as well as the retrospective nature of this study, are limitations of our findings.

Our patient population was at high risk of recurrent VTE events. Of the patients, 28.4% had a diagnosis of hematologic malignancy, which confers a significantly increased risk of primary VTE events compared to low-risk solid tumors; these patients have been excluded from many clinical trials of anticoagulation in patients with cancer due to concern for excess bleeding. Of the patients with solid tumors, 58% had metastatic disease. Despite increased VTE risks in our population, recurrence rates with warfarin are comparable to reported rates for VTE recurrence in general patient populations on warfarin therapy. A recurrence rate of 7% was seen in a prospective observational study of 15 000 patients.[18]

We have found that warfarin can be used successfully to treat VTE in patients with active cancer with acceptable rates of VTE recurrence and bleeding complications, especially in those who have no alternative anticoagulant choices. Our results are similar to a retrospective study in which the rate of recurrent VTE in 145 patients with breast cancer managed by a dedicated AMS was 4.1% with an average TTR of 53%.[19] Warfarin management in patients with cancer is challenging and requires more frequent INR monitoring than in other patient populations, such as those with atrial fibrillation. Drug–drug interactions occur frequently with many chemotherapy regimens,[20] but careful monitoring and dose adjustment by dedicated staff can mitigate significant variations in INR results, as evidenced by our center TTR of 59.5%. Although current ACCP, ASCO, and NCCN guidelines recommend the use of an LMWH for the first 3 to 6 months of treatment of first acute VTE in patients with malignancy,[21–23] for those patients unable to use a parenteral agent, we have demonstrated that warfarin can be used to prevent recurrent VTE events.

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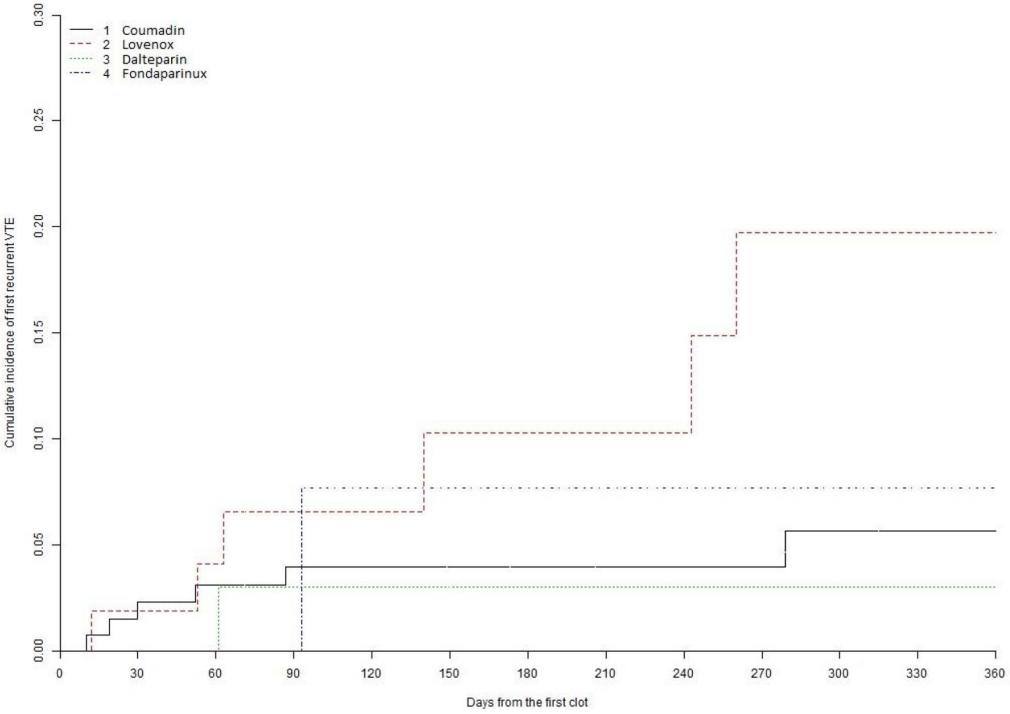

Figure 1.
Incidence of recurrent thrombosis by anticoagulant regimen.

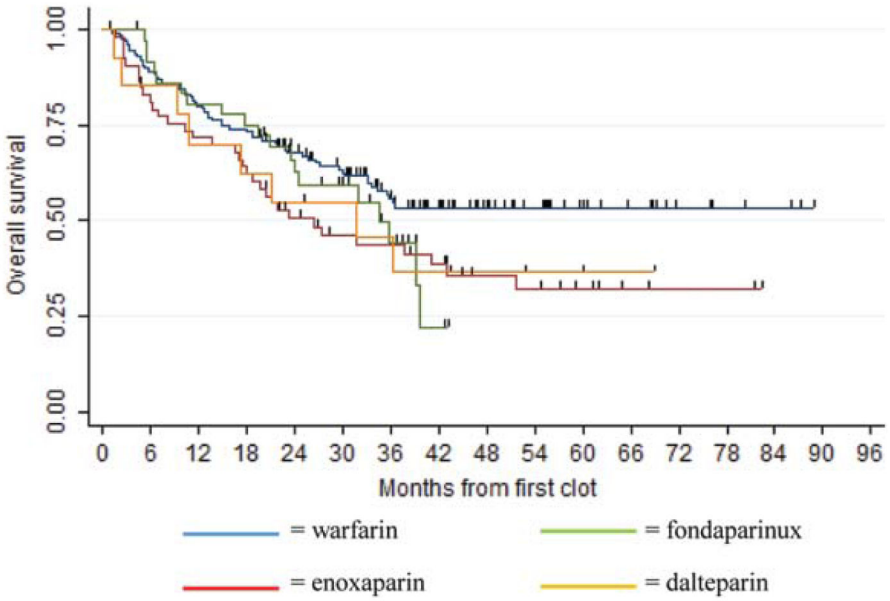

Figure 2.
Kaplan-Meier survival estimates by anticoagulant regimen.

Table 1

Baseline Characteristics.

Age at first clot, median (range)	61.7 (19.5–88.9)
Gender	
Female	136 (57.6%)
Male	100 (42.4%)
Solid Malignancy, n (%)	169 (71.6%)
Breast	30 (17.8%)
Colorectal	24 (14.3%)
Sarcoma	17 (10.1%)
Lung	13 (7.7%)
Ovarian	13 (7.7%)
Bladder	12 (7.1%)
Head and neck	9 (5.3%)
Other	51 (30.2%)
Solid stage, n (%)	
Metastatic	98 (58.0%)
Localized	71 (42.0%)
Hematologic malignancy, n (%)	67 (28.4%)
Non-Hodgkins lymphoma	22 (32.8%)
Multiple myeloma	22 (32.8%)
Hodgkins lymphoma	6 (9.0%)
Chronic lymphocytic leukemia	6 (9.0%)
Acute myeloid leukemia	5 (7.5%)
Other	6 (9.0%)
Transplant (hematologic), n (%)	32 (47.8%)
Initial clot location	
Deep vein thrombosis (DVT)	122 (51.7%)
Pulmonary embolism (PE)	69 (29.2%)
DVT and PE	22 (9.3%)
Inferior vena cava (IVC)	8 (3.4%)
Portal vein	4 (1.7%)
Intracardiac	3 (1.3%)
Intracranial Vein	3 (1.3%)
Gonadal	2 (0.8%)
Other	3 (1.3%)
Initial therapy, n (%)	
Warfarin	132 (55.9%)
Enoxaparin	53 (22.5%)
Dalteparin	37 (15.7%)
Fondaparinux	14 (5.9%)

Table 2

Patient Characteristics and Type of First Anticoagulation.

	Warfarin (N = 132)	Enoxaparin (N = 53)	Dalteparin (N = 37)	Fondaparinux (N = 14)	*P* Value[a]
Age at first clot, median (range)	61.2 (19.5–88.8)	64.2 (25.3–85.4)	61.5 (40.1–85.7)	61.1 (49.0–83.2)	.3887
Gender, n (%)					.7301
Male	53 (40.2%)	26 (49.1%)	15 (40.5%)	6 (42.9%)	
Female	79 (59.9%)	27 (50.9%)	22 (59.5%)	8 (57.1%)	
Initial clot location, n (%)					.7513
DVT	73 (55.3%)	24 (45.3%)	18 (48.7%)	7 (50%)	
PE	32 (24.2%)	21 (39.6%)	11 (29.7%)	5 (35.7%)	
DVT and PE	12 (9.1%)	4 (7.6%)	5 (13.5%)	1 (7.1%)	
Other	15 (11.4%)	4 (7.6%)	3 (8.1%)	1 (7.1%)	
Malignancy type, n (%)					.1663
Solid	90 (68.2%)	36 (67.9%)	31 (83.8%)	12 (85.7%)	
Hematologic	42 (31.8%)	17 (32.1%)	6 (16.2%)	2 (14.3%)	
Solid stage, n (%)					
Localized	41 (45.5%)	17 (47.2%)	9 (29%)	4 (33.3%)	
Metastatic	49 (54.4%)	19 (52.8%)	22 (71%)	8 (67.7%)	
Transplant (hematologic), n (%)					.2079
Yes	17 (40.5%)	9 (52.9%)	5 (83.3%)	1 (50%)	
No	25 (59.5%)	3 (47.1%)	1 (16.7%)	1 (50%)	

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism.

[a] *P* value from Kruskal-Wallis test for age, chi-squared for clot location, and Fisher Exact for all other parameters.

Table 3

Cumulative Incidence of Recurrent VTE During First Anticoagulant by Type of Initial Anticoagulation.

Anticoagulant Regimen	Patients on Regimen	Recurrent VTE, # (%)	3-Month VTE Recurrence, (%)	6-Month VTE Recurrence, (%)	Incidence rate (per 1000 person-months)
Warfarin	132	7 (5.3%)	4.0%	4.0%	4.0
Enoxaparin	53	9 (17.0%)	6.6%	10.3%	24.4
Dalteparin	37	1 (2.7%)	3.0%	3.0%	2.6
Fondaparinux	14	1 (7.1%)	0.0%	7.7%	5.0
Gray test		0.004			

Abbreviation: VTE, venous thromboembolism.

Table 4

Bleeding Episodes During First Anticoagulant by Type of Initial Anticoagulation.

Anticoagulant Regimen	Patients on Regimen	Bleed, # (%)	3-Month Bleed Incidence, (%)	6-Month Bleed Incidence, (%)	Incidence per 1000 Person-Months
Warfarin	132	14 (10.6%)	4 (3.0%)	7 (5.3%)	8.3
Enoxaparin	53	9 (17.0%)	4 (7.5%)	6 (11.3%)	24.7
Dalteparin	37	10 (27.0%)	2 (5.4%)	3 (8.1%)	28
Fondaparinux	14	2 (14.3%)	0 (0.0%)	0 (0.0%)	9.9
Fisher exact		0.089			