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ORIGINAL REPORT

Pattern of Frequent But Nontargeted Pharmacologic Thromboprophylaxis for Hospitalized Patients With Cancer at Academic Medical Centers: A Prospective, Cross-Sectional, Multicenter Study

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ABSTRACT

Purpose
Hospitalized patients with cancer are considered to be at high risk for venous thromboembolism (VTE). Despite strong recommendations in numerous clinical practice guidelines, retrospective studies have shown that pharmacologic thromboprophylaxis is underutilized in hospitalized patients with cancer.

Patients and Methods
We conducted a prospective, cross-sectional study of hospitalized patients with cancer at five academic hospitals to determine prescription rates of thromboprophylaxis and factors influencing its use during hospitalization.

Results
A total of 775 patients with cancer were enrolled across five academic medical centers. Two hundred forty-seven patients (31.9%) had relative contraindications to pharmacologic prophylaxis. Accounting for contraindications to anticoagulation, the overall rate of pharmacologic thromboprophylaxis was 74.2% (95% CI, 70.4% to 78.0%; 392 of 528 patients). Among the patients with cancer without contraindications for anticoagulation, individuals hospitalized with nonhematologic malignancies were significantly more likely to receive pharmacologic thromboprophylaxis than those with hematologic malignancies (odds ratio [OR], 2.34; 95% CI, 1.43 to 3.82; $P = .007$). Patients with cancer admitted for cancer therapy were significantly less likely to receive pharmacologic thromboprophylaxis than those admitted for other reasons (OR, 0.37; 95% CI, 0.22 to 0.61; $P < .001$). Sixty-three percent of patients with cancer classified as low risk, as determined by the Padua Scoring System, received anticoagulant thromboprophylaxis. Among the 136 patients who did not receive anticoagulation, 58.8% were considered to be high risk by the Padua Scoring System.

Conclusion
We conclude that pharmacologic thromboprophylaxis is frequently administered to hospitalized patients with cancer but that nearly one third of patients are considered to have relative contraindications for prophylactic anticoagulation. Pharmacologic thromboprophylaxis in hospitalized patients with cancer is commonly prescribed without regard to the presence or absence of concomitant risk factors for VTE.

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INTRODUCTION

Venous thromboembolic events (VTEs) are a frequent complication of cancer and a significant cause of morbidity and mortality. On the basis of randomized studies demonstrating clear benefit of thromboprophylaxis in acutely ill hospitalized medical patients, the administration of pharmacologic thromboprophylaxis to hospitalized patients with cancer is widely advocated and considered standard practice. Indeed, all major guidelines recommend that hospitalized patients with cancer receive pharmacologic thromboprophylaxis, provided there is no contraindication to anticoagulant use.[1-5]

Despite these recommendations, several population-based studies indicate that the

compliance rates of VTE thromboprophylaxis in inpatients with cancer are low and actually lower than in other high-risk patients who do not have cancer. In an analysis of more than 2.5 million US hospital discharges, hospitalized patients with cancer had the lowest rates of prophylaxis compared with other major medical conditions, including acute myocardial infarction, ischemic stroke, heart failure, and severe lung disease.[6] The published rates of VTE thromboprophylaxis in patients with cancer are largely based on retrospective medical record reviews by using databases of hospitalized patients. We performed a prospective, multicenter, cross-sectional study to evaluate the use of pharmacologic thromboprophylaxis administration and factors influencing this use in hospitalized patients with cancer in several academic medical centers in the United States.

PATIENTS AND METHODS

The protocol was approved by the institutional review boards at each hospital before initiation and in accord with an assurance filed with and approved by the Department of Health and Human Services, where appropriate. Participating sites included Beth Israel Deaconess Medical Center, Johns Hopkins University Medical Center, University of Rochester, University of California Davis Medical Center, and District of Columbia Veterans Administration Medical Center/The George Washington University. Eligible patients were required to have an active hematologic or solid organ malignancy and/or have been previously treated with chemotherapy, surgery, radiation, or biologic or hormonal therapy within the last 6 months. Patients were excluded if they were receiving therapeutic anticoagulation for any reason. Data collection was performed only on patients hospitalized for designated oncology services or inpatient units with de-identified data collected over consecutive days at each site (without treating physicians knowledge) and entered into a central RedCap database. We estimated that approximately 1,000 patients would be enrolled onto the study and, accordingly, the 90% binomial CI width for the estimation of the overall thromboprophylaxis rate in hospitalized patients with cancer would be no wider than 5.3%.

The Padua Prediction Score was calculated for each patient, with a score of ≥ 4 considered higher risk for VTE.[7] Patient characteristics were summarized by using proportions and ranges for binary end points and means and medians along with standard deviations and ranges for continuous end points. Univariable analysis for association of risk factors with the use of pharmacologic thromboprophylaxis was performed by a univariable logistic regression with a two-sided P value. Risk factors identified in the univariable analysis (with $P < .2$) were used in a multivariable stepwise logistic regression model.

RESULTS

Data were collected from 775 patients with cancer across the five medical centers (Table 1) from consecutive patients admitted between January and June 2013. The mean age was 56 years, and 435 patients (46.1%) were men. The mean body mass index was 26.8 kg/m^2, and 204 patients (26.3%) had a body mass index ≥ 30. Four hundred twenty-three patients (54.6%) had hematologic malignancies and 352 patients (45.4%) had solid tumors. Two hundred thirteen patients (60.5%) with solid tumors had metastatic disease. A majority had received chemotherapy or radiotherapy within the last month (505 [62.5%]). Use of erythropoietin-stimulating agents was uncommon (12 patients [1.5%]). The most common reason for hospitalization was chemotherapy or radiation therapy (254 patients [32.8%]) followed by infection (137 patients [17.7%]) and nausea or vomiting (51 patients [6.6%]). The majority of patients with solid tumors (60%) had metastatic disease. Beth Israel Deaconess Medical Center, University of California at Davis, and University of Rochester contributed equally to the data set with 200 patients each, Veterans Administration Medical Center/George Washington University contributed 35 patients, and Johns Hopkins Hospital contributed 140 patients.

Table 1. Demographic and Patient Characteristics (N = 775)

Characteristic	No.	%
Female sex	340	43.9
Age, years		
Mean at admission	56.3	
SD	16.0	
Patients age ≥ 70 years	150	19.4
BMI, kg/m^2		
Mean	26.8	
SD	6.6	
Patients with BMI ≥ 30 kg/m^2	204	26.3
Hematologic malignancy		
Leukemia	224	28.9
Lymphoma (including CNS lymphoma)	149	19.2
Plasma cell dysplasia/multiple myeloma	50	6.5
Total hematologic malignancies	423	54.6
Nonhematologic malignancy		
GI	106	13.7
Lung	54	7.0
Urologic	34	4.4
Sarcoma	30	3.9
Breast	22	2.8
Head and neck	20	2.6
Gynecologic	13	1.7
Primary CNS	12	1.5
Melanoma	8	1.0
Unknown primary	8	1.0
Other	45	5.8
Total nonhematologic malignancies	352	45.4
Metastatic disease/total nonhematologic malignancies	213/352	60.5
Chemotherapy or hormonal treatment within 30 days	505	65.2
Current use of erythropoietin stimulating agents	12	1.5
Reason for hospitalization		
Chemotherapy/radiation/stem-cell transplantation	254	32.8
Infection	137	17.7
Nausea/vomiting/weight loss/dehydration/failure to thrive	51	6.6
Pain management	48	6.2
Oncologic evaluation (eg, diagnosis, recurrence, progression)	45	5.8
Mental status change/delirium	26	3.4
Pulmonary (eg, dyspnea/hypoxia/respiratory failure)	19	2.5
GI bleed	16	2.1
Diarrhea	16	2.1
Other (under 2%)	163	20.9

Abbreviations: BMI, body mass index; SD, standard deviation.

Pharmacologic thromboprophylaxis was administered to 392 of 775 patients (50.6%; 95% CI, 47.0% to 54.2%). Unfractionated heparin was ordered most frequently (61.0%) followed by enoxaparin (37.8%). Two patients received dalteparin and one received fondaparinux. Unfractionated heparin was administered three times daily in 94% of patients (225 of 239) and twice daily in the remaining 14 patients. A total of 247 patients (31.9%) were judged to have relative

Table 2. Relative Contraindications to Pharmacologic Thromboprophylaxis in Hospitalized Patients With Cancer (n = 247)

Contraindication Category	No.*	%
Evidence of significant thrombocytopenia (platelet count < 50,000)	161	65.2
Active hemorrhage	43	17.4
Otherwise considered high risk for hemorrhage (excluding thrombocytopenia)	34	13.8
History of hemorrhage	15	6.1
Patient refusal	12	4.9
Thromboprophylaxis not within goals of care (eg, comfort measures only)	11	4.5
Heparin allergy or heparin-induced thrombocytopenia	2	0.8

*Patients could have more than one contraindication to anticoagulant use.

contraindications to pharmacologic prophylaxis (Table 2). Pharmacologic or mechanical thromboprophylaxis was ordered for 639 patients (82.5%). Accounting for contraindications for anticoagulation, the overall rate of pharmacologic thromboprophylaxis was 74.2% (95% CI, 70.4% to 78.0% [392 of 528 patients]).

Among the group of patients eligible for pharmacologic thromboprophylaxis, 71.4% (377 of 528) were considered high risk by the Padua Scoring System (score ≥ 4), and 78.8% of these patients (297 of 377) received pharmacologic thromboprophylaxis. Twenty-eight percent (151 of 528) were low risk by the Padua Scoring System, and 63% (95 of 151) also received pharmacologic thromboprophylaxis. Of the 136 patients who did not receive anticoagulant prophylaxis but without a contraindication for its use, 58.8% (n = 80) were considered high risk by their Padua Score.

Univariable logistic regression was performed to identify variables predictive of pharmacologic prophylaxis in patients with cancer (Table 3). Among the group of patients without contraindications for thromboprophylaxis, the variables predictive of orders for pharmacologic prophylaxis were increased age (when considered as a continuous variable), solid tumor malignancy, admission for a reason other than chemotherapy or radiation, absence of a central venous catheter, and recent history of trauma or surgery (within the prior 6 months). Individuals with Padua Predictive Score ≥ 4 were more likely to receive anticoagulant prophylaxis compared with individuals with lower-risk scores. Individual elements of the Padua Score that were predictive of pharmacologic thromboprophylaxis were a prior history of VTE, admission with cardiac or respiratory failure, acute infection or rheumatologic disease, and reduced mobility.

Six variables were noted to be predictive of orders for pharmacologic thromboprophylaxis among patients without contraindications for anticoagulation in a multivariable logistic regression (Table 4). The strongest predictor of pharmacologic prophylaxis was a prior history of VTE (odds ratio [OR], 5.8; 95% CI, 2.0 to 17.2). Patients hospitalized with central venous catheters or for cancer-directed therapy (ie, chemotherapy or radiation) were less likely to receive thromboprophylaxis. A high overall Padua Predictive Score (≥ 4) was not independently associated with increased odds of receiving anticoagulant prophylaxis in this model ($P = .07$).

Although the absolute rate of thromboprophylaxis varied between sites (ranging from 42% to 95%), this variation appeared to reflect differences in patient characteristics of the patients admitted during the study period rather than differences in practice patterns.

Table 3. Univariable Analysis of the Use of Pharmacologic Thromboprophylaxis in Patients With Cancer and No Contraindications for Anticoagulation (n = 528)

Risk Factor	Total No.	Total %	Among Patients Receiving Pharmacologic Prophylaxis No.	Among Patients Receiving Pharmacologic Prophylaxis %	*P*
Age, years					< .001
Median	59		61		
Range	18-93		20-93		
Disease type (solid tumors)	270	51.1	233	86.3	< .001
Admission for cancer therapy (chemotherapy or radiation)	178	33.7	94	52.8	< .001
Central venous catheter	327	61.9	220	67.3	< .001
Trauma or surgery within last 6 months	140	26.5	115	82.1	.013
Chemotherapy or hormonal therapy within last 30 days	345	65.3	262	75.9	.221
Female sex	229	43.4	174	76.0	.424
BMI, kg/m^2					
Median			25.6		
Range			13.7-59.0		.558
Current use of erythropoietin–stimulating agents	5	0.9	4	80.0	.767
Current inferior vena cava filter	11	2.1	11	100.0	.984
Padua score risk factors					
Acute infection/rheumatologic disorder	165	31.3	139	84.2	.005
Reduced mobility	54	10.2	48	88.9	.013
Prior history of VTE	58	11.0	54	93.1	.002
Cardiac/respiratory failure	49	9.3	43	87.8	.028
Elderly age (≥ 70 years)	109	20.6	87	79.8	.137
Trauma/surgery within last 30 days	39	7.4	32	82.1	.251
Obesity (BMI ≥ 30 kg/m^2)	128	24.2	99	77.3	.357
Known thrombophilia	0	0	—		—
Active hormone therapy	21	4.0	16	76.2	.835
Acute myocardial infarction or ischemic stroke	5	0.9	5	100.0	.983
Padua score (≥ 4)	377	71.4	297	78.8	< .001

Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

The magnitude and significance of the six predictors of thromboprophylaxis use were not substantially affected by inclusion of all the individual sites in the stepwise regression model. For instance, the OR for pharmacologic thromboprophylaxis for patients admitted for cancer therapy versus other reasons was 0.24 ($P < .001$) when individual

Table 4. Variables Predictive of Pharmacologic Thromboprophylaxis in Hospitalized Patients With Cancer by Multivariable Logistic Regression

Variable	OR	95% CI	*P*
History of prior VTE *v* no history	5.80	1.96 to 17.18	.002
Nonhematologic *v* hematologic malignancy	2.34	1.43 to 3.82	< .001
Acute infection or rheumatologic disorder *v* other diagnosis	1.92	1.12 to 3.31	.018
Trauma or surgery within last 6 months *v* none	1.74	1.011 to 2.99	.046
Admission for cancer therapy *v* another reason	0.37	0.22 to 0.61	< .001
Central venous catheter *v* none	0.56	0.34 to 0.95	.031

Abbreviations: OR, odds ratio; VTE, venous thromboembolism.

sites were included in the regression model compared with 0.37 ($P <$ .001) when they were not. The same holds true for all the other variables predictive of pharmacologic thromboprophylaxis (Table 4), such as solid tumor versus hematologic malignancy (OR, 2.9; $P <$ .001), history of prior VTE (OR, 4.44; $P = .01$), trauma within 6 months (OR, 2.09; $P = .02$), and central venous catheter (OR, 0.57; $P = .05$).

DISCUSSION

Pharmacologic thromboprophylaxis is recommended for all patients with hospitalized cancer without contraindications.[1-5] Despite a mandate from the Joint Commission and National Quality Forum for inpatient anticoagulant thromboprophylaxis, the reported rates of adherence are low, especially in cancer populations, with thromboprophylaxis use ranging widely from 18% to 56% of patients.[6,8-12] By comparison, in this multicenter, cross-sectional study, the documented use of anticoagulant thromboprophylaxis was 74% among patients with cancer considered eligible for anticoagulation.

Data collection methodology may, in part, explain differences in our data compared with previously published thromboprophylaxis rates. The predominance of data published on thromboprophylaxis compliance is based on retrospective analysis of large databases. Although the algorithmic cross-referencing of anticoagulants with cancer diagnosis is straightforward, an accurate determination of why patients do not receive anticoagulant thromboprophylaxis is more difficult. In this study, real-time data collection resulted in 32% of patients with all cancer types considered inappropriate for pharmacologic prophylaxis because of a variety of factors, including history of hemorrhage, patient refusal, and daily injections not considered within the goals of care. The proportion of patients with contraindications in our study was much higher than reported in other database-driven studies. Whether the reason for withholding pharmacologic prophylaxis was indeed appropriate on a per-patient basis was not assessed in this study. However, it is difficult to set absolute thresholds for pharmacologic thromboprophylaxis in cancer cohorts. Patients with cancer who receive anticoagulation are known to be at an increased risk of hemorrhage relative to other patient populations,[13] and cancer itself is considered an independent risk factor for in-hospital hemorrhage.[14] Per published guidelines, withholding thromboprophylaxis is advised if the physician considers the patient at an increased risk of hemorrhage.[4]

The participating sites in this study broadly represent the spectrum of US academic centers in terms of size, National Cancer Institute–designated cancer sites, minority populations served, oncology trial participation, and National Institutes of Health research support. The magnitude and significance of the six predictors of thromboprophylaxis use were not substantially affected by the adjustment for individual sites in the stepwise regression model, suggesting that overall practice patterns are generalizable across academic institutions. Admittedly, the applicability of these data to community-based hospital practices is not known.

We identified several variables that influenced the probability of receiving pharmacologic thromboprophylaxis in hospitalized patients with cancer. Not surprisingly, patients with a prior history of thrombosis were most likely to receive pharmacologic thromboprophylaxis. However, other variables that influence the decision to use anticoagulant prophylaxis are less readily justified by the current literature. Patients with hematologic malignancies were less likely to receive thromboprophylaxis despite documented rates of venous thromboembolic events that were equal to or higher than those of many solid tumors.[15,16] Similarly, the use of chemotherapy is an established risk factor for thrombosis,[15] but patients were less likely to have received pharmacologic thromboprophylaxis in this setting compared with hospitalization for other reasons such as acute infection. These data help to identify which populations of patients with cancer may be targeted for improved rates of thromboprophylaxis.

The common perception is that hospitalized patients, especially those with cancer, require pharmacologic thromboprophylaxis, as evidenced by the high rate of thromboprophylaxis in this study. However, a more measured approach to inpatient pharmacologic thromboprophylaxis is advocated,[4,17] especially in a patient population considered high risk for in-hospital hemorrhage.[14] The Padua Prediction Score was developed to identify hospitalized patients considered highest risk for thrombosis,[7] and its use is advocated by the authors of the ninth edition of the Antithrombotic Therapy and Prevention of Thrombosis guidelines published by the American College of Chest Physicians.[4] The diagnosis of cancer is an element of the scoring system, and thus the majority of the patients included in this study were considered higher risk. Although elements of the scoring system, such as recent surgery or active infection, appear to influence the decision to use anticoagulant prophylaxis, a high Padua score was not independently associated with increased likelihood of prophylactic anticoagulation by multivariable analysis. Indeed, nearly two thirds of patients with lower-risk cancer also received pharmacologic thromboprophylaxis. The ACCP Guidelines advise against the use of thromboprophylaxis in such lower-risk patients.[4]

The recommendation to prescribe pharmacologic thromboprophylaxis for inpatients with cancer is based on data derived from large clinical trials of hospitalized medical patients that demonstrated efficacy in reducing the overall incidence of VTEs.[18-20] However, among the 5,134 patients enrolled onto three randomized clinical trials that assessed the efficacy of low-molecular-weight heparins or fondaparinux, only 307 (6%) were diagnosed with cancer, and in a recent meta-analysis, no statistical reduction in overall incidence of VTEs was demonstrated.[21] The lack of efficacy lends further support for the notion that not all patients with cancer should be considered at equal risk for thrombosis—many patients with cancer enrolled onto these studies were at lower risk of thrombosis and thus did not benefit from anticoagulation whereas others suffered thrombotic events despite pharmacologic thromboprophylaxis. Higher doses of anticoagulants or longer duration prophylaxis may be required in cases of increased thrombotic risk associated with malignancy.

On the basis of the results of this study, it is apparent that the majority of patients with cancer admitted to these five academic medical centers in the United States receive pharmacologic thromboprophylaxis. However, in the quest for strict compliance with federal mandates and competency measures and for minimizing legal liabilities, the lack of evidence supporting a one-size-fits-all approach to thromboprophylaxis for inpatients with cancer has been overlooked. These data bring into focus the deficiencies in both current clinical practice and evidence. There are little data to suggest that patients with a lower risk of cancer benefit from routine thromboprophylaxis. As advocated in the updated guidelines issued by the American Society of

Clinical Oncology,[17] additional assessments are needed to identify which patients with cancer with concomitant risk factors justify the use of (up to thrice) daily injectable anticoagulant, especially in a population considered at increased risk for in-hospital hemorrhage. Outcome studies are needed to further optimize pharmacologic thromboprophylaxis for inpatients with cancer; however, in the interim it is important that health systems and physicians be aware that current standard practice requires attention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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