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Factors influencing the use of thromboprophylaxis in cancer outpatients in clinical practice: A prospective study

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ABSTRACT

Introduction: Current clinical practice guidelines do not recommend routine pharmacological thromboprophylaxis in cancer outpatients receiving chemotherapy. However, a high proportion of cancer-associated venous thromboembolism (VTE) events occur in this setting. There are scarce data on the use of thromboprophylaxis in ambulatory cancer patients in real clinical practice.

Material and methods: We conducted a single-center prospective study aimed to evaluate the use and factors influencing pharmacological prophylaxis in consecutive cancer patients receiving ambulatory chemotherapy. Patients were followed for 90 days after inclusion.

Results: A total of 1108 patients were included. According to the Khorana score, 45.8% patients were classified as low-risk, 47.4% intermediate-risk and 6.8% as high-risk. Outpatient pharmacological prophylaxis was administered at any time during follow-up to 157 patients (14.2%) with a median duration of 42 days (range 1–90). Main factors influencing thromboprophylaxis were: previous history of VTE (odds ratio [OR], 19.11; 95% CI, 9.61–37.98), intercurrent hospitalization (OR, 5.40; 95% CI, 3.57–8.16), and gastrointestinal or gynecologic cancer (OR, 1.76; 95% CI, 1.11–2.80 and OR, 2.34; 95% CI, 1.05–5.26, respectively). During follow-up 58 (5.2%) VTE events were observed. Independent predictors of VTE were the site of malignancy (OR, 3.04; 95%CI, 1.20–7.71 and OR, 2.47; 95%CI, 1.21–5.01 for pancreas and lung cancer, respectively) and previous VTE (OR, 4.23; 95%CI, 1.26–14.27). Outpatient prophylaxis was associated with a lower risk of VTE during follow-up (OR, 0.30; 95%CI, 0.10–0.95).

Conclusions: Although the type of malignancy appears as the most relevant variable for decision-making, additional efforts are required to identify patients at particular high thrombosis risk.

1. Introduction

Venous thromboembolism (VTE) is a frequent complication in cancer patients with important consequences in terms of morbidity, mortality and consumption of health resources. Indeed, hospitalization is a well-known risk factor for VTE among cancer patients [1]. Although current evidence-based clinical practice guidelines recommend pharmacological prophylaxis (mainly with low molecular weight heparin, LMWH) in hospitalized cancer patients with any other risk factor unless contraindicated [2–4], several studies have shown an alarming underuse [5–7].

On the other hand, a number of VTE episodes develop in ambulatory cancer patients receiving treatment with chemotherapy or other antineoplastic agents. Two recent large randomized clinical trials (PROTECHT and SAVE-ONCO) evaluated the efficacy and safety of nadroparin and semuloparin for VTE prevention in cancer outpatients. Although pharmacological prophylaxis was associated with a statistically significant relative reduction of thrombotic events, the impact in absolute terms was modest [8–9]. Therefore, most current guidelines do not recommend routine thromboprophylaxis in this setting (except for multiple myeloma patients treated with immunomodulatory drugs) [2–4,10]. However, subgroup analyses of the previous studies suggested that the benefit/risk ratio could favor prophylaxis if targeted to high-risk cancer patients [11].

To date, the scale developed by Khorana et al. (Khorana score) is the only validated tool for risk stratification of cancer outpatients starting chemotherapy [12], although its positive predictive value is low. The

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combination of the Khorana score with plasma biomarkers such as D-dimer or P-selectin could improve the predictive value of the score [13], although standardization appears as a main concern that limits its general application.

Some studies have addressed the use of pharmacological thromboprophylaxis and factors influencing its use in hospitalized cancer patients in real world practice [5–7], but to date there are scarce data in cancer outpatients. We have performed a prospective study to evaluate the use of pharmacological prophylaxis and factors influencing its use in cancer patients receiving ambulatory chemotherapy treatment in an academic center.

2. Material and methods

Consecutive adult patients (age ≥ 18 years old) with an active hematologic or solid organ malignancy receiving systemic antineoplastic treatment at the Oncology-Hematology Day Hospital of the Clínica Universidad de Navarra (Spain) were included. Patients receiving therapeutic anticoagulation for any reason were excluded.

The study was approved by the institutional investigation and ethics committees, before initiation. At inclusion, data collection of demographic characteristics, risk factors for VTE and blood tests results was performed using a software linked to our Clinical Records System, which is fully electronic. This software had been previously used for the implementation of an electronic alert system in hospitalized patients [14] and was adapted for the assessment of cancer outpatients.

Patients were followed for 90 days after inclusion. The use and duration of pharmacological prophylaxis, need of hospitalization, incidence of objectively diagnosed VTE, either upper or lower limb deep vein thrombosis (DVT), pulmonary embolism (PE) or thrombosis at other locations, and major or clinically relevant bleeding during follow-up were obtained through medical records review or by telephone interview. Bleeding was defined as major if it was overt and associated with a decrease in the hemoglobin level of 2 g per deciliter or more, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death [15]. Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, or discomfort or impairment in carrying out activities of daily life. Patients could be included only once during study.

Categorical variables were expressed as frequencies and percentages, and quantitative variables as either mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution. Univariate analysis for association of risk factors with the use of thromboprophylaxis and the risk of VTE was performed by univariate logistic regression, with a two-sided p value. Risk factors identified in the univariate analysis ($p < 0.05$) were included in a multivariable logistic regression model. Analyses were performed using SPSS 20.0, WinPepi 13 and ENE 3.0 softwares.

3. Results

Between November 2008 and December 2010, 1108 patients were included in the study (Table 1). Mean age was 58 ± 12.1 years and 544 (49.1%) were men. Most patients (1056; 95.3%) had solid organ tumors, gastrointestinal, breast and lung malignancies being the most frequent. Five hundred and seven patients (45.8%) had metastatic disease. In 496 patients (44.8%) the diagnosis of cancer had been reached in the previous three months and 507 patients (45.8%) had not received any chemotherapy before inclusion. A long-term central vein catheter had been placed in 229 patients (20.7%). Granulocyte-colony stimulating factor (G-CSF) was prescribed in 23.9% of the patients, while the use of erythropoietin stimulating agents was uncommon (1.2%). Regarding other risk factors for VTE, 346 patients (31.2%) had been hospitalized and 176 (15.9%) had undergone surgery in the previous month before inclusion. Fifty-three subjects (4.8%) had a past medical history of VTE.

Table 1
Patients' characteristics (N = 1108).

Characteristics	N (%)
Age (years); mean (SD)	58 (12.1)
Male sex	544 (49.1)
Body mass index (kg/m^2) >30	177 (16.0)
Tumor site	
Gastrointestinal	310 (28.0)
Breast	232 (20.9)
Lung	153 (13.8)
Gynecological	76 (6.9)
Urological	67 (6.0)
Pancreas	62 (5.6)
Head/neck	54 (4.9)
Hematological	52 (4.7)
Central nervous system	47 (4.2)
Skin	25 (2.3)
Other	30 (2.7)
Metastatic disease	507 (45.8)
Recent diagnosis (previous 3 months)	496 (44.8)
No previous chemotherapy	507 (45.8)
Lines of chemotherapy; median (range)	1 (1–8)
Use of long-term central venous catheter	229 (20.7)
Current use of erythropoietin stimulating agents	13 (1.2)
Current use of G-CSF	264 (23.9)
Recent hospitalization (previous month)	346 (31.2)
Recent surgery (previous month)	176 (15.9)
Recent immobilization (>3 days)	43 (3.9)
Other chronic comorbidities (COPD, CCF)	59 (5.3)
Previous history of VTE	53 (4.8)
Known thrombophilia	2 (0.2)
Hb (at inclusion); mean (SD)	12.5 (1.7)
White cells/mm^3 (at inclusion); mean (SD)	7.1 (4.2)
Platelets/mm^3 (at inclusion); mean (SD)	267 (110)

According to the Khorana score, 505 (45.8%) patients were classified as low-risk, 523 (47.4%) corresponded to the intermediate-risk category and 75 patients (6.8%) were categorized as high-risk patients. In five patients the Khorana score could not be calculated.

Overall, pharmacological prophylaxis, consisting in all cases of once-daily LMWH, was administered to 264 patients (23.8%) at any time during follow-up. However, in 107 patients (40.5% of those receiving any prophylaxis) LMWH was indicated exclusively during an intercurrent hospitalization. Therefore, 157 patients (14.2%) received pharmacological thromboprophylaxis as outpatients; 66 of 505 (13.1%) in the low-risk group, 75 of 523 (14.3%) in the intermediate-risk group, and 15 of 75 (20.0%) in the high-risk group. Median duration of prophylaxis was 42 days (range 1–90).

Factors associated with increased use of pharmacological prophylaxis in the univariate analysis are shown in Table 2. In our series, the Khorana risk category was not significantly associated with a higher prescription of LMWH ($p = 0.13$). After multivariable logistic regression (Table 3), the strongest predictors of thromboprophylaxis indication

Table 2
Factors influencing thromboprophylaxis use in ambulatory cancer patients. Univariate analysis.

Characteristics	Odds ratio (OR)	95% CI	p
Age (years)	1.02	1.00–1.03	0.008
Age (>70)	1.67	1.10–2.54	0.017
Tumor site			
Gastrointestinal	2.46	1.74–3.48	<0.001
Breast	0.36	0.20–0.62	<0.001
Gynecologic	1.84	1.04–3.24	0.036
Hematologic	0.23	0.06–0.96	0.045
No previous chemotherapy	1.53	1.08–2.14	0.015
Use of long-term CVC	0.52	0.32–0.85	0.009
Recent surgery	0.56	0.33–0.97	0.037
Past history of VTE	9.53	5.37–16.92	<0.001
Intercurrent hospitalization	5.46	3.83–7.77	<0.001

CVC: central venous catheter.