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Original article

Breast cancer-associated venous thromboembolism: A case–control study

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ABSTRACT

Breast cancer is frequently associated with venous thromboembolism (VTE). VTE may result in significant morbidity, a substantial economic burden and even leads to patients' death. Risk factor identification and management of VTE in breast cancer patients remains poorly studied. We evaluated breast cancer patients' baseline and treatment characteristics in predicting VTE occurrence as well as its prognosis.

We conducted a case–control study of all breast cancer patients with a VTE diagnosed between January 2007 and December 2011 at the *Instituto Nacional de Câncer* (INCA) in Brazil.

Two hundred and twenty five patients developed VTE and were compared with 225 controls, in the 5-year study period. The bulk of the thrombotic events were unilateral (94.2%) VTEs of the lower extremity (78.7%), largely proximally located (78%). VTE occurred more often within the first 3 years after the diagnosis of cancer (66.2%), being more common in the first 6 months (21.8%). Significant predictors of developing VTE were age 50 years and over (OR 1.85, 95% CI: 1.16–2.95), PS equal to or above 3 (OR 2.01, 95% CI: 1.24–3.26), and the presence of a CVC (OR 2.56, 95% CI: 1.42–4.62).

This large retrospective analysis of VTE in breast cancer patients confirms that most events occur early in the treatment course. The incidence of VTE was associated with patients' age, PS, and the presence of CVC. Prospective studies are needed to evaluate outpatient thromboprophylaxis for selected groups of patients.

Introduction

The association between thromboembolism and cancer was first reported in 1865 by Armand Trousseau and since then it has been supported by a large body of data [1]. Patients with cancer are at a four- to sevenfold higher risk of venous thromboembolism (VTE) than patients without a malignancy [2]. Changes in the hemostatic system and evidence of chronic hemostatic activation are frequently observed in cancer patients, even in the absence of VTE [3].

VTE risk factors can be patient-related (age, obesity, performance status [PS], comorbidities), cancer-related (tumor type, site and stage), or treatment-related (use of chemotherapy, anti-angiogenic agents or hormonal treatment, surgery, presence of a central venous catheter [CVC], and hospitalization) [4]. A better understanding of the interaction between all these components is key to identifying patient subgroups that might benefit from preventive strategies.

Although there is a clear benefit for hospitalized cancer patients, outpatient thromboprophylaxis remains controversial [5–7]. The Khorana score is a simple model for predicting outpatient chemotherapy-associated VTE using baseline clinical and laboratory variables that has been validated. Five predictive variables were identified: site of cancer, platelet count, hemoglobin level or use of erythropoiesis-stimulating agents, leukocyte count and body mass index [8].

VTEs are associated with significant morbidity and they are a leading cause of death in cancer patients [9–11]. Moreover, patients with cancer experience increased VTE recurrences and bleeding complications while on anticoagulation therapy, when compared with those without cancer [3]. In addition, VTEs result in a need for hospitalization and a substantial economic burden [12].

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The risk of VTE is not uniform across cancer types. Although breast cancer carries a relative low VTE risk (1–2.8% 2-year cumulative rate) when compared with other tumor types, VTE in breast cancer patients is a common and important clinical problem due to the high prevalence of this tumor [13]. Notwithstanding, risk factor identification and management of VTE in breast cancer patients remains poorly studied. We evaluated breast cancer patients' baseline and treatment characteristics in predicting VTE occurrence as well as its prognosis in a large Brazilian academic hospital.

Patients and methods

We conducted a case–control study of all breast cancer patients with a VTE diagnosed between January 2007 and December 2011 at the *Instituto Nacional de Câncer* (INCA) in Brazil. Cases were patients with the diagnosis of a deep venous thrombosis (DVT) or a pulmonary embolism (PE) during the study period. A DVT was ascertained based on color Doppler ultrasonography performed by a single investigator (MEFC) during the study period. A PE was confirmed by contrast-enhanced computerized tomography (CT), with specific protocol for this. As cases of VTE were identified retrospectively, thus leading to potential loss of some cases, we searched the hospital pharmacy records for use of anticoagulant agents, which would suggest the occurrence of a VTE. Further investigation of patient charts was conducted to confirm this occurrence among patients who had any anticoagulant prescribed during the study period, retrieving 32 additional cases. The control group consisted of unmatched breast cancer patients (selected on a 1:1 ratio *vis-à-vis* cases) that had a suspected DVT but a color Doppler ultrasonography without such finding during the same time frame.

The univariate association between VTE and baseline clinical variables was initially characterized using chi-square tests. Variables found to be significant ($P < 0.10$) by univariate analysis were subsequently entered into a multivariate stepwise logistic regression model with VTE as the response variable. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Women were followed up until death or December 31, 2011, whichever came first. Overall survival was defined as the time from date of VTE diagnosis to date of death due to any cause. The Cox proportional hazards model was used to determine the adjusted risk of death as a function of VTE. Statistical analysis was performed using SPSS software for Windows® (version 13.0; SPSS Inc., Chicago, IL, US), and two-sided P values < 0.05 were considered statistically significant.

Results

Patient characteristics

Two hundred and twenty five patients developed VTE and were compared with 225 controls, in the 5-year study period (Fig. 1). Patients' baseline and treatment characteristics at the time of VTE diagnosis are listed in Table 1. The bulk of the thrombotic events were unilateral (94.2%) VTEs of the lower extremity (78.7%) largely proximally located (78%). VTE were more likely to occur within the first 3 years after the diagnosis of cancer (66.2%), being more common in the first 6 months (21.8%) (Fig. 2). Warfarin was the usual long-term anticoagulant treatment (81.8%) followed by a low molecular weight heparin (LMWH) (15.1%) and unfractionated heparin (UFH) (0.4%). As per physicians' discretion, forty-five percent of patients had their cancer treatment changed due to VTE, mostly while on tamoxifen.

Univariate predictors of venous thrombosis

Significant predictors of developing VTE were age 50 years and over, Eastern Cooperative Oncology Group (ECOG) PS equal to or above 3, the presence of a CVC and Disease status (no evidence of disease versus partial response, stable disease or disease progression) ($P = 0.047$, $P = 0.028$, $P = 0.004$, and $P = 0.021$, respectively). A previous episode of thrombosis achieved P values of 0.054. There were a wide variety of systemic treatments, all of them with a small sample size, which showed no association with a VTE. We found no significant association between the Khorana Risk Score and VTE.

Multivariate predictors of venous thrombosis

In multivariate models, three of the factors identified in the univariate analyses above, namely age 50 years and over (OR 1.85, 95% CI: 1.16 to 2.95), PS equal to or above 3 (OR 2.01, 95% CI: 1.24 to 3.26), and the presence of a CVC (OR 2.56, 95% CI: 1.42 to 4.62), were found to be independent risk factors for VTE (Table 2).

Survival

At a median follow-up of 15.4 months, the median overall survival from the VTE was 27.0 months for patients with a VTE and it had not been reached in the control group. However, after Cox regression and adjustment for other covariates, this difference was no longer statistically significant (HR 1.10, 95% CI 0.82–1.45, $P = 0.54$).

Discussion

In this large retrospective analysis performed at an academic hospital, we identified 225 breast cancer patients who developed VTE, during a 5-year period. Most thromboembolic events were unilateral (94%) DVTs of the lower extremity (79%) and more than one fifth of all the events (22%) occurred within the initial 6 months after cancer diagnosis. Forty-five percent of patients had their systemic cancer treatment changed due to a VTE. Age 50 years and

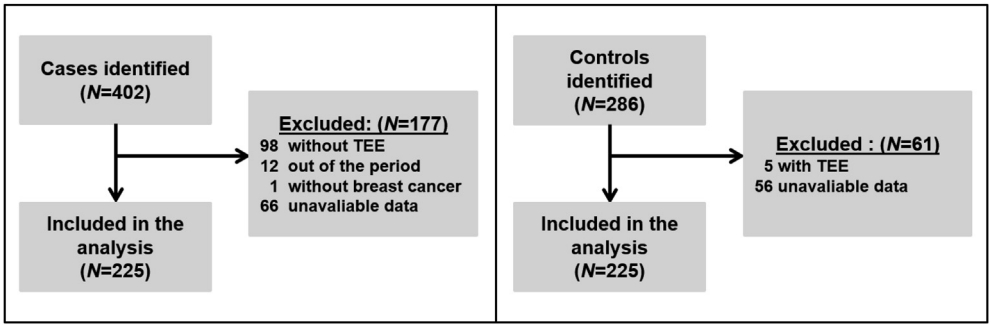

Fig. 1. Patient identification and selection. TEE, thromboembolic event.