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Incidence and risk factors of symptomatic venous thromboembolism related to implanted ports in cancer patients

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ABSTRACT

Introduction: The true incidence of symptomatic implanted port related venous thromboembolism (VTE) in cancer patients is unclear and there is very limited data on its associated risk factors.
Materials and methods: We performed a retrospective cohort study of consecutive cancer outpatients who received an ultrasound guided implanted port insertion for the administration of chemotherapy. The primary outcome measure was symptomatic VTE. Univariable and multivariable logistic regression analyses were used to identify risk factors for symptomatic VTE.
Results: A total of 400 cancer patients with a newly inserted implanted port for deliverance of chemotherapy were included in the study. Median age was 58 years (range of 21 to 85 years) and 120 (30%) were males. Patients were followed for a median of 12 months and none received thrombophrophylaxis. Of the 400 patients included in the analysis, 34 patients (8.5%; 95% CI: 6.0 to 11.7%) had symptomatic VTE (16 DVTs, 16 PEs, and 2 with both). In the univariate analyses, metastatic disease, male gender and right sided implanted port insertion were significantly associated with the risk of VTE. In the multiple-variable analysis, male gender (OR 2.17, $p = 0.04$) and presence of metastases (OR 8.22, $p < 0.01$) were the two significant independent predictors of implanted port related VTE.
Conclusion: Symptomatic VTE is a frequent complication in cancer patients with implanted port receiving chemotherapy. Gender and presence of metastatic disease are independent risk factors for symptomatic VTE. Future trials assessing the role of thromboprophylaxis among these higher risk patients are needed.

Background

Central venous catheters such as implanted ports are widely used in cancer patients for convenient administration of chemotherapy [1,2]. These devices improve patient's quality of life and reduce health care costs by allowing patients to receive chemotherapy at home [3]. Thrombosis is a common complication of catheters and is associated with significant morbidity [4]. Many studies have reported potential risk factors of catheter-associated deep vein thrombosis (DVT) [5]. However, the reliability of the data is limited by small sample sizes, few catheter-associated DVT events, variability in duration of follow-up, and heterogeneity in the outcome definitions [6].Therefore, there is uncertainty about the risk factors and the true incidence of catheter-associated DVT. There is also an uncertainty about the need for thromboprophylaxis for catheter-associated DVT [7–10]. The most recent American College of Chest Physicians (ACCP) guidelines suggest against routine prophylactic with low molecular weight heparin (Grade 2B) or vitamin K antagonists (Grade 2C) [11]. Furthermore, the most recent international practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer also recommend against use of anticoagulation for routine thromboprophylaxis [12]. While previous studies have included patients with various types of catheters, very little data is available on risk factors associated with symptomatic venous thromboembolism (VTE) related specifically to implanted ports. Moreover, although previous studies have examined the complications associated with implanted port insertion, the data evaluating the clinical importance of symptomatic implanted port-related VTE is scarce [13–19].

Given the limited available data, we sought to evaluate the incidence of symptomatic implanted port-related VTE and to establish the risk factors most predictive of developing implanted port related thrombosis in cancer patients undergoing chemotherapy.

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Materials and methods

Inclusion and exclusion criteria

A retrospective cohort study of consecutive cancer patients who received an ultrasound-guided implanted port for the administration of chemotherapy between November 2010 and December 2011 was conducted at the Ottawa Hospital. This period was chosen to establish a post insertion follow-up period of at least 6 months for all patients. In our center, all technical details of insertion were documented in a central database ensuring all consecutive cancer patients were included. Patients were included if they met the following criteria: 1) documented active malignancy; 2) implanted port insertion; and 3) undergoing systematic chemotherapy or adjuvant chemotherapy. Patients were excluded if they received either therapeutic or prophylactic anticoagulation at time of implanted port insertion. No routine thrombophrophylaxis was used while the implanted port was in situ. All implanted ports were inserted by interventional radiologists using an ultrasound guided internal jugular approach with fluoroscopy to confirm placement. All patients received the same model of implanted port (X-port ISP, Bard Access Systems Inc, Salt Lake City, US).

Baseline characteristics

Demographic, clinical, and laboratory characteristics were collected, including factors previously suggested as being predictive of cancer-associated and catheter-related DVT: gender, age, body mass index (BMI), smoking status, side of implanted port insertion, tip location (cavo-atrial junction or distal superior vena cava or mid-superior vena cava or atrium), tip location on chest radiography performed within 1 month post insertion, presence of metastases, previous VTE, hemoglobin, platelet count, creatinine, estimated glomerular filtration rate (e-GFR), and co-morbidities of hypertension, coronary artery disease, chronic obstructive lung disease (COPD), diabetes mellitus, chronic kidney disease, dementia, and implanted port associated infection or bacteremia. Presence of diabetes mellitus was defined as documented prior history thereof or use of anti-hyperglycemic agents or insulin. Data were extracted independently by two investigators (S.P. and V.N.). Disagreements on information were resolved either by consensus or through retrieving further information from other medical records. All patients were followed for a minimum of 6 months post implanted port insertion unless they died during the follow-up period. The primary outcome measure was symptomatic VTE. Venous thromboembolism was defined has symptomatic upper extremity implanted port related proximal (axillary vein or more proximal) DVT or pulmonary embolism (PE).

Statistical analyses

Kaplan-Meier method was used to calculate the cumulative incidence of implanted port-associated VTE. Univariable and multivariable logistic regression analyses were used to calculate unadjusted and adjusted odds ratios and their 95% confidence intervals for symptomatic VTE. Variables that satisfied statistical significance of $p < 0.1$ in a univariable analysis were retained in the multivariable model. These risk factors included gender, side of catheter insertion, and presence of metastases. Analyses were performed using the SAS, version 9.0 (SAS institute, North Carolina).

Results

A total of 400 consecutive cancer patients obtained an implanted port for deliverance of chemotherapy and met our inclusion criteria. Eighty nine patients were excluded based on our exclusion criteria. The median age was 58 years (range of 21 to 85 years) and 120 (30%) were males (see Table 1). The most common cancer type was breast cancer (47.5%). Of the 400 patients enrolled, 38 (9.5%) patients were taking aspirin during the follow-up period. All patients were followed for a median of 12 months (range of 6 to 23 months) and none received thrombophrophylaxis.

Table 1
Baseline Characteristics.

Characteristic	No Event (N = 366)	Symptomatic Implanted port-related VTE (N = 34)
Age (Median; years)	57.9	59.5
Gender – Male (N;%)	102 (28)	18 (53)
Primary Malignancy (N, %)		
Lung	6 (1.6)	0 (0)
Ovary	11 (3)	2 (5.9)
Brain	1 (0.27)	0 (0)
Breast	183 (50)	7 (20.6)
Gastrointestinal Tract	148 (40.4)	21 (61.7)
Prostate	3 (0.82)	0 (0)
Hematological	5 (1.37)	1 (2.94)
Other	9 (2.46)	3 (8.22)
BMI (Median; Kg/m^2)	26.3	27.6
Smokers (N;%)	54 (15.2)	7 (20.6)
Left-Sided Catheter (N;%)	62 (16.94)	1 (2.94)
Tip Location (N;%)		
Cavoatrial junction	221 (60.5)	20 (58.8)
Distal SVC	135 (37)	14 (41.2)
Middle SVC	1 (0.27)	0 (0)
Proximal SVC	0 (0)	0 (0)
Atrium	8 (2.2)	0 (0)
Co-morbidities (N;%)		
Metastases	221 (60.4)	32 (94.1)
Hypertension	122 (33.3)	14 (41.2)
Coronary Artery Disease	22 (6)	1 (2.9)
COPD	12 (3.3)	1 (2.9)
Diabetes	36 (9.8)	3 (8.8)
Hemoglobin (Mean; g/L)	126	124
eGFR (Median; ml/min)	84	79

BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; eGFR: Estimated Glomerular Filtration Rate; SVC: Superior Vena Cava; VTE: Venous Thromboembolism

Of the 400 patients enrolled, 34 patients (8.5%; 95% CI: 6.0 to 11.7%) had symptomatic VTE (16 upper extremity DVTs, 16 PEs, and 2 with both). The most common tip location at the time of VTE was the cavoatrial junction in 59% of cases (20/34) followed by distal SVC in 41% (14/34). Seventeen of the 18 implanted port-associated DVTs were ipsilateral to the implanted port and one patient had bilateral upper extremity DVTs. The median time from insertion of implanted port to VTE occurrence was 103 days (range of 13 to 371 days). Fig. 1 shows that the cumulative incidence of symptomatic implanted port related VTE increases over time.

Of the 34 patients with a symptomatic VTE, all were initially treated with low molecular weight heparin and 9 had an implanted port removal (completion of treatment ($n = 4$); erosion into the skin ($n = 1$); and other ($n = 4$)). Of the 18 patients that developed PE, 5 deaths occurred and none were attributed to VTE. Moreover, 6 of the 34 patients with a symptomatic implanted port-related VTE also had a lower extremity DVT (5 patients with a PE and one patient with both a PE and an implanted port-associated DVT).

In the univariable analysis, male gender independent of the type of cancer was significantly associated with the risk of VTE (OR 2.94, $p = 0.0032$) (Table 2). Of the catheter characteristics, right sided implanted port insertion was significantly associated with the risk of VTE (OR 6.66, $p = 0.06$). Furthermore, presence of metastatic disease was also a significant contributor (OR 10.5, $p = 0.0014$). The most common cancer types were gastrointestinal (GI) tract cancer (62%) in patients with a symptomatic VTE and breast cancer (50%) was more frequent in patients without VTE. Multivariable analysis was performed using male gender, right sided implanted port insertion, and presence of metastases (Table 2). Male Gender (OR 2.17, $p = 0.04$) and presence of metastases (OR 8.22, $p < 0.01$) were the