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Full Length Article

A prospective study of Rivaroxaban for central venous catheter associated upper extremity deep vein thrombosis in cancer patients (Catheter 2)

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ABSTRACT

Introduction: Patients with cancer are at increased risk of thrombosis, particularly those with central venous catheter (CVC) placement, which may predispose to the development of upper extremity deep vein thrombosis (UEDVT). Standard treatment includes low molecular weight heparin (LMWH) or LMWH bridged to warfarin. The direct oral anticoagulants (DOACs) have become standard of care for uncomplicated venous thromboembolism (VTE), but research in patients with cancer is ongoing.
Objectives: To assess rivaroxaban monotherapy in patients with cancer who develop UEDVT due to CVC for preservation of line function, and safety outcomes of VTE recurrence, bleeding risk and death.
Materials and methods: Patients ≥18 years of age with active malignancy and symptomatic proximal UEDVT with or without pulmonary embolism (PE), associated with a CVC, were eligible. Treatment included rivaroxaban 15 mg oral twice daily for 3 weeks, followed by 20 mg oral daily for 9 weeks. Patients were followed clinically for 12 weeks to assess for line function, recurrent VTE and bleeding.
Results: Seventy patients (47 women) were included, with mean age 54.1 years. The most common malignancy was breast cancer (41%). Preservation of line function was 100% at 12 weeks. The risk of recurrent VTE at 12 weeks was 1.43%, with one episode of fatal PE. 9 patients (12.9%) experienced 11 total bleeding episodes.
Conclusions: Rivaroxaban showed promise in treating CVC-UEDVT in cancer patients, resulting in preserved line function. However, bleeding rates and a fatal pulmonary embolism on treatment are concerning safety outcomes necessitating further study before rivaroxaban can be recommended.

1. Introduction

Upper extremity deep vein thrombosis (UEDVT) constitutes 4–10% of cases of deep vein thrombosis (DVT) [1]. Various studies examining secondary events after UEDVT have found a lower incidence of concurrent pulmonary embolism (PE), venous thromboembolism (VTE) recurrence and post thrombotic syndrome compared with DVT of the lower extremity [2]. UEDVT is frequently associated with central venous catheter (CVC) placement and cancer in 70% and 40% of patients respectively [3]. However, treatment in patients with cancer can be challenging with a recent systematic review demonstrating a 2–3 fold higher risk of recurrence, 8 fold increased risk of mortality and 4 fold increased risk of bleeding in patients with malignancy vs. no malignancy [1].

Management options for UEDVT are based primarily on trials in lower extremity DVT and PE [1]. There are no previous randomized controlled trials for UEDVT. Additionally, trials showing the superiority of low molecular weight heparin (LMWH) over vitamin K antagonists (VKA) for cancer associated thrombosis (CAT) specifically excluded patients with UEDVT, including those associated with a CVC [4–6]. We previously showed that dalteparin bridged to warfarin was successful in 74 patients over 12 weeks of therapy with no recurrent VTE events, a 4.7% bleeding rate similar to other cancer associated thrombosis trials at short term follow up [7], and no episodes of CVC infusion failure. Therefore, treatment for these patients may include LMWH bridged to warfarin or LMWH monotherapy, generally without line removal unless the

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line is no longer required, is defective or non-functional, or infection is present [8].

The direct oral anticoagulants (DOACs), including the thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, have emerged in recent years for treatment of acute, symptomatic VTE demonstrating non-inferior efficacy and superiority in bleeding outcomes [9–11]. Additional benefits include fixed dosing, fewer drug and food interactions, and no requirement for blood level monitoring as compared to warfarin. Rivaroxaban was approved for treatment of VTE in 2012 based on the results from the EINSTEIN-DVT and EINSTEIN-PE trials [12,13]. Subgroup analysis of these trials has suggested that safety and efficacy of rivaroxaban is preserved in cancer-associated VTE, although exclusion criteria selected for healthier patients, and those with active cancer at trial enrollment or during treatment accounted for only 8% of their total population [14].

The purpose of this study was to prospectively evaluate the safety and efficacy of rivaroxaban in the treatment of UEDVT secondary to CVC in patients with cancer.

2. Materials and methods

2.1. Patients

This was a prospective multicentre cohort study. Consecutive patients 18 years of age or older with active malignancy (ie. receiving active treatment, having metastatic disease or having been diagnosed within the past 2 years) not including non-melanoma skin cancer, and symptomatic proximal UEDVT (axillary or more proximal) with or without PE, associated with a CVC, were eligible. Objective documentation of thrombosis by compression ultrasonography, venogram or computed tomography (CT) scan was required. Patients were ineligible if they had one or more of the following criteria: the catheter was a dialysis catheter; active bleeding; platelet count $<75 \times 10^9$/L; creatinine clearance <30 mL/min; on another anticoagulant(s) with therapeutic intent for another indication; PE with hemodynamic instability; inability to infuse through the catheter after a trial of intraluminal thrombolytic therapy (tissue plasminogen activator, tPa); patients with acute leukemia or multiple myeloma with a bone marrow or stem cell transplant planned within 3 months; thrombosis involving the brachial, basilic or cephalic veins only; treatment for >7 days with another anticoagulant; need for dual antiplatelet therapy (recent coronary stent); or concomitant use of P-glycoprotein and CYP3A4 inhibitors.

The study protocol was reviewed and approved by the institutional ethics board of each centre. Written, informed consent was obtained from all patients.

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2.2. Treatment protocol

After obtaining written informed consent, patients were treated with rivaroxaban at a dose of 15 mg orally twice daily for 3 weeks, followed by 20 mg daily for 9 weeks. Anticoagulation was continued for 12 weeks regardless of the length of time the catheter was in place. Continuation of anticoagulation beyond this time period was at the discretion of the investigators. This study allowed the use of tPa for management of blocked lines. Patients were followed in the thrombosis clinic at 1, 4 and 12 weeks, and by phone at 6 months, to assess for primary and secondary outcomes.

2.3. Outcome measures

The primary efficacy outcome was preservation of line function at 3 months, with loss including infusion failure that did not respond to 2 mg of tPa in addition to the physical removal of the CVC. Secondary outcomes included symptomatic recurrent VTE, defined as objectively documented recurrent VTE or death attributable to PE, major bleeding and clinically relevant non-major bleeding (CRNMB), and death from all causes. The criteria for recurrent PE or DVT, and bleeding events have been defined previously [15,16]. All events were independently adjudicated.

2.4. Statistics

The previous Catheter study [17] showed that no patients had catheter failure. We therefore estimated that a sample size of 72 patients produced a one-sided 98% upper-limit confidence interval with a distance from the sample proportion to the upper limit that is equal to 0.04994 when the sample proportion is 0. That is, this sample size would allow to detect a proportion within a 95% confidence interval between 0 and 5%. In secondary analysis we evaluated the survival time of the catheter using survival analysis according to the Kaplan-Maier method. Patients were censored at the end of the observation period, death of the patient, or catheter removal due to end of therapeutic need or patient request but not due to line failure. Potential predictors of catheter failure were explored using Cox proportional hazard analysis. P values <0.05 were considered significant. All analyses were done using SPSS Statistics v21 (IBM Corp., Armonk NY).

3. Results

3.1. Patient Demographics

70 patients (47 [67%] women) were enrolled at three centres in Canada between December 2012 and January 2016 (Table 1). The mean age was 54.1 years. UEDVT was diagnosed by ultrasound in 68 (97%) patients, and most commonly involved the subclavian ($n = 55$, 79%) and axillary ($n = 49$, 70%) veins, followed by the internal jugular, brachial, brachiocephalic and external jugular veins. Peripherally inserted central catheters (PICC) were most common ($n = 54$, 77%), followed by port-a-cath lines ($n = 16$, 23%). Types of active malignancy included breast ($n = 29$, 41%), colon ($n = 8$, 11%), colorectal ($n = 5$, 7%), rectal ($n = 3$, 4%), prostate ($n = 1$, 1%), and other ($n = 24$, 34%). 51% received LMWH prior to rivaroxaban, with 24 and 12 patients receiving enoxaparin and dalteparin respectively, at therapeutic doses prior to enrollment.

3.2. Main outcome

58.6% (95% confidence interval (CI), 46.9 to 69.4) of catheters were in place at 12 weeks and no catheters were removed due to infusion failure. Thus preservation of line function was 100%. Patients had their

Table 1
Patient demographics.

Variable	Description, n (%)
Gender	Female, $n = 47$ (67.1)
Median age	54.1 years
Diagnostic modality	Ultrasound, $n = 68$ (97.1)
Vein involvement	Subclavian, $n = 55$ (78.6)
	Axillary, $n = 49$ (70.0)
	Internal jugular, $n = 18$ (25.7)
	Others: Brachial, brachiocephalic, external jugular veins
CVC type	Peripherally Inserted Central Catheter (PICC), $n = 54$ (77.1)
	Port-a-cath, $n = 16$ (22.9)
Type of cancer	Breast, $n = 29$ (41.4)
	Colon, $n = 8$ (11.4)
	Colorectal, $n = 5$ (7.1)
	Rectal, $n = 3$ (4.3)
	Ovarian, $n = 5$ (7.1)
	Other, $n = 20$ (28.6)
Received LMWH before?	Yes, $n = 36$ (51.4)

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