A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study)

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Summary. Background: Central venous catheters in patients with cancer are associated with development of deep vein thrombosis (DVT); however, there is no accepted standard treatment. Objectives: To assess the safety and effectiveness of a management strategy for central venous catheter-related DVT in cancer patients consisting of dalteparin and warfarin without the need for line removal. Patients/methods: Patients older than 18 years of age with an active malignancy and who had symptomatic, acute, objectively documented UEDVT were eligible. Patients were treated with dalteparin 200 IU kg\(^{-1}\) per day for 5–7 days and warfarin with a target International Normalized Ratio of 2.0–3.0. Patients were followed for 3 months for recurrent venous thromboembolism, major hemorrhage and survival of the central venous catheter. Results: There were 74 patients (48 males). The average age was 58 years. There were no episodes of recurrent venous thromboembolism and three (4%) major bleeds. No lines were removed because of infusion failure or recurrence/extension of DVT. Conclusion: Treatment of UEDVTs secondary to central catheters in cancer patients with standard dalteparin/warfarin can allow the central line to remain in situ with little risk of line failure or recurrence/extension of the DVT.

Keywords: cancer, central venous catheter, low-molecular-weight heparin, treatment, upper extremity deep vein thrombosis.

Introduction

Venous thromboembolism is a common complication in patients with cancer [1,2]. One to 5 per cent of cases of venous thromboembolism occur in the upper extremity [3]. In patients with cancer, upper extremity deep vein thrombosis (UEDVT) occurs most commonly while there is an indwelling central venous catheter [4]. The clinical presentation of UEDVT is variable and therefore, as with lower extremity DVT, objective criteria supporting the diagnosis should be sought before initiating therapy. Contrast venography, allowing for direct visualization of the whole deep vein system of the arm, is the gold standard for the diagnosis of UEDVT but several non-invasive methods have also been successfully used as alternatives to venography techniques. These include real-time compression ultrasonography, duplex ultrasonography and color doppler ultrasonography [3–7]. A recent study has helped to clarify the ultrasound criteria for the diagnosis of UEDVT [8]. A DVT can be diagnosed if there is a non-compressible venous segment, if there is a visible intraluminal thrombus or if there is an abnormal flow pattern [8].

Historically, central venous catheters in cancer patients have been associated with a risk of UEDVT of 5–10%, although recent studies suggest the risk of thrombotic complications may be only 2–5% [9–15].

The management of patients who develop an UEDVT secondary to a central venous catheter is not standardized. Management options have included thrombolytic therapy, immediate line removal, standard anticoagulation with unfractionated heparin or low-molecular-weight heparin (LMWH), and oral anticoagulant therapy. For most patients, if the line is removed, there is still a need for central venous access but a ‘replacement’ central venous catheter will be at risk of further thrombotic complications. Moreover, the thrombosis associated with the original central venous catheter still
needs to be managed with anticoagulant therapy [4]. Hence, as most cancer patients with UEDVT because of a central venous catheter still require central venous access, and require anticoagulation, it may be inappropriate to remove the catheter.

The purpose of this multi-centre cohort study was to prospectively assess the efficacy of a management strategy for central venous catheter-associated UEDVT in cancer patients that consists of salvage (i.e. non-removal) of the central venous catheter in association with treatment of the UEDVT with LMWH overlapped and followed by oral anticoagulation with warfarin for 3 months.

**Methods**

**Patients**

Consecutive adult (greater than or equal to 18 years of age) patients with a diagnosis of active malignancy (receiving active treatment, having metastatic disease or having been diagnosed within the past 2 years), who had symptomatic, acute UEDVT with or without pulmonary embolism associated with a central venous catheter (documented by compression ultrasound, venogram or contrast CT scan) were eligible. Patients with an incidental finding of UEDVT on imaging without symptoms were not eligible. Patients were excluded if they had one or more of the following: the catheter was a dialysis catheter, active bleeding or high risk for major bleeding, platelet count less than $100 \times 10^9 \text{ L}^{-1}$, serum creatinine greater than $177 \mu \text{mol L}^{-1}$, currently on warfarin with therapeutic intent (not including mini-dose warfarin used as prophylaxis for catheter thrombosis), pulmonary embolism accompanied by hemodynamic instability or oxygen requirement, inability to infuse through the catheter including after a trial of intraluminal thrombolytic therapy (2 mg tissue plasminogen activator [tPA]) (that is, the catheter must have been functional), or patients with acute leukemia with a bone marrow or stem cell transplant pending in the next 3 months.

The study protocol was reviewed and approved by the institutional review boards of each participating center. Written, informed consent was obtained from all patients. At the time of consent, all patients were registered with the coordinating center. The study was supported by an unrestricted grant from Pfizer Canada (ClinicalTrials.Gov NCT00216866).

**Treatment protocol**

Patients were treated with dalteparin 200 IU kg$^{-1}$ s.c. once a day for a minimum of 5 days and until the International Normalized Ratio (INR) was $>2.0$. Oral anticoagulation with warfarin was initiated usually on the first day using a nomogram of proven efficacy [16]. The INR was maintained at 2.0–3.0 for the duration of the study. If a catheter lumen developed an infusion or aspiration blockage, participating centers were instructed to administer 1–2 mg tPA up to two times per blocked lumen to attempt to unblock the catheter.

**Patient follow-up**

While receiving dalteparin injections, patients were assessed daily, usually by telephone (most patients were managed as outpatients) unless the patient was hospitalized, in which case the study nurse visited the patient. Patients were seen subsequently at 7, 28 and 90 days after study enrollment. Management after 3 months was left to the discretion of the attending physician.

**Outcome measures**

The primary efficacy endpoint of the study was the rate of central line failure, defined as infusion failure that did not respond to 2 mg tPA (which could be administered twice) or removal of the line because of progressive or recurrent venous thromboembolism within the 3-month follow-up period. Secondary endpoints included recurrent venous thromboembolism (objectively diagnosed based on previous criteria [16]), major bleeding (defined according to previous criteria [16]), and death during 3-month follow-up. All outcome events were subject to independent central adjudication.

**Statistical analysis**

The study hypothesis was that at least 80% of patients would be treated successfully without the need for removal of the catheter because of progressive or recurrent thrombosis. The sample size was determined to be 70 patients, based on feasibility of recruitment in the participating centers over a 2-year period and to allow for a reasonably precise estimate of the rate of central line failure and the respective 95% confidence limits.

Outcomes were assessed on an intent-to-treat basis for all consenting subjects. Removal of catheters prior to the 3-month study endpoint because of end of therapeutic need or patient request and not because of line failure or recurrent thrombosis were considered as censored events after the time of removal but not as study endpoints.

**Results**

**Patients**

Seventy-four patients (48 males) were enrolled at four centers between November 2002 and December 2005. The average age was 58 years. Seventy-one were diagnosed by compression ultrasound and three by contrast CT scan. The majority of the central venous catheters were PICC lines ($n = 57; 77\%$). There were 14 portacaths (19%) and three Hickman catheters (4%). Only five patients (6.8%) had had a previous catheter. Twenty-two (29.7%) patients were receiving mini-dose warfarin (none had prolonged INRs) at the time of diagnosis. The most proximal veins involved are listed in Table 1.
related outcomes. With dalteparin monotherapy and did not have any catheter-first day against study protocol, while two patients were treated were not evaluable; one patient had the line removed on the shock and ropinH bada today31(INR>5.5). Three patients day 34 after a major hemorrhage presenting as hypovolemic endometrial cancer died while receiving compassionate care at

Discussion
This prospective cohort study has demonstrated that central venous catheter associated UEDVT in cancer patients can be successfully treated with a standard approach of dalteparin and warfarin with the catheter still functional until the end of therapeutic need or 3 months (whichever occurs first). The efficacy of our management strategy based on our predetermined criteria was 100%. Despite leaving the catheter in place there were no episodes of recurrent venous thromboembolism. Two catheters were removed because of infection; however, they did not have symptoms or ultrasound evidence for DVT.

We have previously demonstrated the efficacy of dalteparin and warfarin for the treatment of UEDVT in outpatients [4]. This study focused exclusively on cancer patients with central venous catheters. Currently there is a wide range of approaches to this problem, many of which include immediate removal of the central catheter. Most of these patients still have a therapeutic need for a central catheter. Removal of a central venous catheter in this situation does not obviate the need for treatment of the UEDVT that is still in situ after the catheter is removed. An approach such as ours treats the UEDVT and allows the catheter to remain in place.

There were three episodes of major hemorrhage in our study patients, one of which resulted in death. Although the major hemorrhage rate was 4%, which is higher than one would expect for patients without cancer, it is comparable with previously published bleeding rates in cancer patients with DVT of the lower extremities or pulmonary embolism [16,17]. Moreover, because of the presence of a symptomatic UEDVT these patients require anticoagulation for a minimum of 3 months whether the line is removed or not.

The Clot Study has previously reported on the superiority of monotherapy with dalteparin compared with the standard protocol employed in this study for cancer patients with pulmonary embolism or DVT of the lower extremity [16,17]. In that study the recurrent venous thromboembolism rate on the warfarin arm was 17% at 6 months vs. 0% in 74 patients at 3 months in our study. The most likely reason for this difference is that UEDVT in our study were catheter associated and hence were secondary clots that were likely to have a better prognosis (i.e. lower risk of recurrence) even when treated in the standard fashion with LMWH followed by warfarin. The results of our study suggest that monotherapy with LMWH for catheter-associated UEDVT in cancer patients may not be necessary for treatment efficacy; however, other reasons such as patient preference or poor venous access for INR monitoring may influence the treatment choice.

Limitations of our study include the small sample size, and the fact that there is no comparison group. Also, 32 patients had their catheters removed prior to the 3-month endpoint, although none were removed because of thrombosis and most of those were removed because of an end of therapeutic need. This study could, however, serve as a basis for future larger randomized studies. However, a randomized study of line removal vs. no line removal would be logistically difficult and would, of course, be impossible to blind.

This study suggests that for the majority of cancer patients with UEDVT in association with central venous catheters,
treatment of the DVT in a standard fashion with dalteparin and warfarin will allow continued function of the central venous catheter without recurrent venous thromboembolism in most patients. Automatic removal of a functioning central venous catheter at the time of diagnosis of UEDVT would appear to be unnecessary.

Addendum

M. J. Kovacs was the principal investigator. S. R. Kahn, M. Rodger, D. R. Anderson, R. Andreou, J. E. Mangel and P. S. Wells enrolled patients and had input into the design. R. Andreou co-authored the original protocol with Dr Kovacs. B. Morrow and A. M. Clement were the coordinators of the study.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References