Home-treatment of deep vein thrombosis in patients with cancer

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Background and Objectives. Outpatient treatment of deep vein thrombosis (DVT) has become a common practice. However, in some centers cancer patients with DVT are excluded from home treatment because they have a higher risk of both bleeding and recurrent DVT. We performed a retrospective review of clinical practice patterns to assess the rate of cancer patients who were deemed eligible for outpatient treatment of their DVT.

Design and Methods. The charts of patients from the Thrombosis Units at two tertiary care institutions were reviewed. All patients with objectively documented DVT at our institutions are treated through the Thrombosis Units. Patients are treated as outpatients unless they require admission for other medical problems, are actively bleeding or have pain that requires parenteral narcotics. Outpatient treatment was with low molecular weight heparin (LMWH) followed by warfarin or with LMWH alone.

Results. Over a period of almost four years there were 321 patients with cancer, 167 (52.5%) of whom had metastatic disease. The most frequent sites of cancer were genitourinary tract (21.2%), breast (20.5%), and gastrointestinal system (18.4%). Treatment with LMWH and warfarin was prescribed to 67% and LMWH alone to 33%. One hundred and ninety-seven patients (61.4%) were entirely treated at home. There were no differences between patients treated at home and hospitalized patients with regard to gender, mean age, site of cancer, presence of metastases, and treatment. After 3 months, recurrent thromboembolism occurred in 6.1% of patients treated at home and in 4.8% of hospitalized patients (p=0.64), and major bleeding in 1.0% and 4.8%, respectively (p=0.03). One hundred and sixty patients died (49.8%), 100 (50.7%) in the home treatment group and 60 (48.4%) of the hospitalized patients.

Interpretation and Conclusions. Home treatment of DVT in cancer patients is safe and feasible in almost two-thirds of cases. Outpatient management of antithrombotic treatment did not increase the rate of adverse events, even if the stage of the disease was advanced.

Key words: venous thromboembolism, cancer, home treatment

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Cancer is one of the most common causes of venous thromboembolism (VTE). The prevalence of known cancer ranges from 10 to 20% at the time when VTE is diagnosed.[1] Treatment of VTE in cancer patients is problematic because of a two- to threefold higher risk of recurrence despite conventional anticoagulant therapy and because of an increased risk of bleeding complications.[2-4]

Home treatment of deep vein thrombosis (DVT) is a common practice in many European and North American centers. Two large clinical trials[5,6] clearly showed the efficacy and safety of low molecular weight heparins (LMWH) in the outpatient setting, and a number of reports from clinical practice[7,8] or further comparisons between in-hospital and home treatment[9] have subsequently confirmed the practicality of home treatment of DVT. Despite this evidence, rates of hospitalization of patients with acute DVT vary among countries and remain high in many centers. Social factors and the lack of a clear consensus on concomitant clinical conditions that should mandate in-hospital treatment are the main reasons for such differences. Home treatment of patients with underlying malignancies has been reported,[7,8,10,11] but to our knowledge there are no studies that specifically report on the safety and feasibility of the outpatient management of acute DVT in patients with cancer. Patients with cancer often have concomitant medical problems that complicate initial anticoagulation care and thus suggest hospitalization for DVT treatment would be preferable. On the other hand, these patients may be inclined towards home-treatment because of a

potential positive impact on their quality of life. When the choice between home treatment and hospitalization was offered to cancer patients with acute DVT who were clinically eligible for outpatient management, 100% chose home treatment.[12] This suggests that provided home treatment is safe it should be considered for all cancer patients.

In this study we assessed the feasibility of home treatment of acute DVT in cancer patients and compared the outcomes in the hospitalized and home-treated patients.

Design and Methods

The charts of patients with objectively documented DVT and active cancer (ongoing or palliative) who were referred to the Thrombosis Unit of the Ospedale di Circolo of Varese, Varese, Italy from February 2000 to June 2003 and to the Ottawa Hospital General Campus Thrombosis Unit, Ottawa, Canada from January 1999 to December 2003 were reviewed. Data on 22 patients referred to the Thrombosis Unit of Varese in the years 2000 and 2001 were previously published as a part of a prospective cohort study.[11]

All patients presenting with acute DVT, diagnosed by means of compression ultrasound or venography, are routinely evaluated for the home treatment program at both institutions. Usually, the following criteria are applied for hospital admission: illness that independently requires hospitalization, high risk of bleeding or active bleeding, pain requiring parenteral narcotics, likelihood of poor compliance, or refusal of home treatment. Patients selected for the home treatment program are provided with teaching on the treatment and potential complications of venous thromboembolism by either the attending physician or a clinic nurse. Patients or care-givers are taught how to perform the injections and are given an explanation of oral anticoagulant therapy, with particular emphasis on bleeding risks and the importance of regular monitoring. The same education is provided to the hospitalized patients at the time of discharge.

Treatment was provided in two ways: (i) full dose subcutaneous, weight-adjusted, once or twice daily LMWH (enoxaparin, dalteparin, or nadroparin) for a minimum of 5 days with concomitant warfarin, with LMWH discontinued when the international normalized ratio (INR) reached the therapeutic range (2.0 to 3.0) for two consecutive days. Warfarin was started within 24 hours of diagnosis. INR monitoring and subsequent dosage adjustments were performed daily for hospitalized patients, after 2 or 3 days and then according to individual needs for the outpatients. In both centers warfarin treatment was monitored by the institutional Anticoagulation Clinic with INR monitoring according to individual needs but with a maximum of four weeks between INR measurements. The follow–up lasted three months; (ii) LMWH was administered for the entire three-month treatment period. LMWH was administered in a full therapeutic dose for the first month and at 50% to 75% of the full dose during the second and third months. No predefined criteria were used to select one of the two treatment modalities. At both institutions, patients were encouraged to call the units if symptoms of DVT or pulmonary embolism worsened or developed, if bleeding was observed, if new medications were started or if any invasive procedures were planned. All patients underwent an assessment at the Thrombosis Unit after 3 months.

Assessments

We collected data on the patients' age, gender, site of DVT, concomitant, objectively confirmed symptomatic pulmonary embolism, time between diagnosis of cancer and diagnosis of DVT, site of cancer, presence of metastases and the specifics of cancer treatment. For hospitalized patients, the reason for admission and the mean duration of stay were documented. Details of the antithrombotic treatment were obtained, rates of recurrent DVT or pulmonary embolism, major or minor bleeding, and mortality at 3 months were also collected. Recurrent DVT was defined as the detection of a new thrombus or the extension of the previous thrombus documented by compression ultrasound. For pulmonary embolism, high probability lung scans or filling defects on contrast spiral computed tomographic scans were diagnostic. An intermediate probability lung scan was considered diagnostic of acute pulmonary embolism if a new thrombosis was also found on compression ultrasonography of the legs and the patient had appropriate pulmonary symptoms. Bleeding was defined as major if it was intracranial or retroperitoneal, or if it was overt and associated with either a decrease in hemoglobin levels of at least 2.0 g/dL or a need for the transfusion of at least 2 units of packed red blood cells. Bleeding was defined as minor if it was overt but did not meet the criteria for major bleeding.

The following characteristics were subsequently compared between outpatients and hospitalized patients: age, gender, site of DVT, concomitant symptomatic pulmonary embolism, site of cancer, presence of known metastases, and concomitant ongoing therapies for cancer. The rates of recurrent VTE, major and minor bleeding events and death at 3 months were the outcome measures compared

between outpatients and inpatients. The mean age of the patients and the mean time between diagnosis of cancer and diagnosis of DVT were compared by t tests, all other comparisons were performed by χ^2 tests. A p value lower than 0.05 was considered statistically significant.

Results

We identified 321 patients with cancer and an objectively documented acute DVT. Their baseline characteristics are summarized in Table 1, separately for patients treated at home or in hospital. The mean time between diagnosis of cancer and DVT was 25.4 months, the most common site of cancer was the genitourinary tract, and 52.5% of patients had known metastases at the time of DVT diagnosis. Cancer treatment was ongoing in 59.5% of patients, most of whom were receiving chemotherapy. One hundred and ninety-seven patients were entirely treated at home (61.4%). For the 124 (38.6%) patients who required hospitalization, the mean hospital stay was 11.6 days. The most common reasons cited for hospital admission were investigation of recurrent cancer (n=49), concomitant medical disorder (n=24), concomitant pulmonary embolism (n=13), concomitant DVT in other sites (n=9), illness that independently required hospitalization (n=8), and pain requiring parenteral narcotics (n=5). Treatment with LMWH and warfarin was administered to 215 patients (67%), LMWH alone was administered to the remaining 106 patients (33%). Considering both the outpatients and hospitalized patients, recurrent DVT or pulmonary embolism occurred in 18 patients (5.6%), major bleeding in 5 patients (1.5%), and minor bleeding in 10 patients (3.1%). One hundred and sixty patients (49.8%) died during the 3-month follow-up. Comparing the outpatients and the hospitalized patients the rate of recurrent venous thromboembolic events was similar (6.1% vs 4.8% respectively; p=0.64) but major bleeding events occurred more commonly in hospitalized patients (1.0% vs 4.8%; p=0.03). The mortality rate was high in both groups but there was no statistical difference between the groups (Table 2).

When we compared patients treated at home with patients treated in hospital, we found no differences according to gender and mean age. Patients with distal DVT were more likely to be treated at home (35% and 24.2%, respectively, p=0.04), whereas patients with concomitant pulmonary embolism were more likely to be hospitalized (11.7% and 21.8%, respectively, p=0.015). Patients with upper limb DVT or with bilateral lower limb DVT were equally distributed in the two groups. The tumor type/origin and the proportion of patients with metastatic disease were similar between patients treated at home and patients treated in hospital. There was no difference in the mean time interval between cancer diagnosis and DVT diagnosis in the two groups. Of interest, patients receiving chemotherapy at the time of DVT

Table 1. Baseline characteristics and cancer site and stage for outpatients and inpatients.

	Outpatients	*Inpatients*
Number	197	124
Male gender, n(%)	74 (37.5%)	55 (44.3%)
Age (mean), years	60.0	61.1
Age (range), years	16-93	16-87
Concomitant pulmonary embolism, n(%)	23 (11.7%)	27 (21.8%)
Mean time from cancer to DVT diagnosis	26.6 months	23.4 months
Site, n(%)		
Genitourinary	39 (19.8%)	29 (23.4%)
Breast	45 (22.8%)	21 (16.9%)
Gastrointestinal	39 (19.8%)	20 (16.1%)
Lung	31 (15.7%)	24 (19.3%)
Hematologic	20 (10.1%)	11 (8.9%)
Brain	9 (4.6%)	6 (4.8%)
Other	14 (7.1%)	14 (11.3%)
Metastases	106 (53.8%)	61 (49.2%)
Ongoing chemotherapy*	103/194 (53.1%)	44/123 (35.8%)
Ongoing radiotherapy*	33/194 (17%)	15/122 (12.3%)
Ongoing hormone therapy*	28/196 (14.3%)	16/123 (13%)
LMWH/Warfarin	131 (66.5%)	84 (67.7%)
LMWH alone	66 (33.5%)	40 (32.3%)

**Information on concomitant therapy was not available for all patients.*

Table 2. Outcome events at 3 months.

	Outpatients	*Inpatients*
Number	197	124
Recurrent VTE	12* (6.1%)	6°(4.8%)
Major bleeding	2 (1.0%)	6 (4.8%)
Minor bleeding	4 (2.0%)	6 (4.8%)
Mortality	100 (50.7%)	60 (48.4%)

*VTE: venous thromboembolism; *11 events were proximal DVT and 1 was pulmonary embolism; °5 events were proximal DVT and 1 was pulmonary embolism.*

diagnosis were more likely to be treated at home than to be admitted to hospital (p=0.0107). Finally, there was no difference in antithrombotic treatment between the 2 groups.

Discussion

Our results support the feasibility of providing home treatment to most patients with active cancer who present with acute DVT. In our experience, nearly two-thirds of patients with malignancy can be managed entirely as outpatients regardless of age, site of cancer, presence of known metastases, and ongoing cancer treatment. The predominant reasons for providing treatment in hospital were the need to investigate for recurrent cancer, or because of concomitant medical problems usually related to complications of the cancer. Recurrent venous thromboembolic rates were similar in the two groups. Major hemorrhage was more frequent in the hospitalized patients but this is to be expected given that active bleeding and a high risk of bleeding were reasons for exclusion from home treatment. The rate of patients with serious clinical conditions was high in both groups, as shown by the nearly identical rate of patients with metastases and the high mortality rate. Despite this being a seriously ill group of patients, home treatment of DVT was at least as safe and effective as in-hospital treatment.

To our knowledge, this is the first study that has specifically addressed the initial outpatient management of DVT in cancer patients. We believe that cancer patients can derive important benefits from outpatient treatment because a new hospital admission can negatively affect their quality of life. However, cancer is frequently considered a criterion for exclusion from home treatment of DVT and in many centers these patients are routinely admitted to hospital. In a previous study,[11] we observed that 43% of hospital admissions for acute DVT were due to concomitant malignancy. This study confirms that despite a higher risk of recurrent venous thromboembolic events or hemorrhagic events in cancer patients, outpatient management of DVT is possible in the majority, even if life expectancy is short. Based on the results of our study, patients with less extensive disease, in particular patients without concomitant pulmonary embolism, and patients with ongoing chemotherapy were the best candidates for the outpatient treatment.

Our study has limitations. The retrospective design and lack of randomization weakens the strength of our findings and makes comparisons of event rates less reliable. However, all patients were regularly followed-up at both institutions and the pertinent information was routinely collected. Although the study is retrospective the data were collected prospectively. Moreover, the management of these patients was similar in the two centers. The mortality rate was high and we cannot confirm how many deaths were due to unsuspected pulmonary embolism but the attending physicians did not record pulmonary embolism as a suspected cause of death and the death rates were similar in both the hospitalized and outpatient therapy groups.

The results of our study support the initial home treatment management of many cancer patients with acute DVT, and should promote this approach in more institutions. The results of a recent randomized controlled trial in which dalteparin was used for six months for the antithrombotic management of DVT in cancer patients may further increase the feasibility of outpatient management by enabling elimination of the need for INR monitoring.[13] Furthermore, dalteparin was shown to be significantly more effective than oral anticoagulants in reducing the risk of recurrent VTE without increasing the risk of bleeding. Oral anticoagulants are particularly problematic in cancer patients because of interactions with several chemotherapies, because of poor venous access or poor clinical conditions that can make laboratory monitoring difficult, and because of more cumbersome management in the case of bleeding or invasive procedures. Many patients are commonly hospitalized for strict monitoring of the induction phase of oral anticoagulant treatment when receiving chemotherapy or due to concomitant illness that makes ambulatory INR monitoring unfeasible.

In conclusion, we found that most patients with active malignancy and acute DVT can be safely and effectively treated at home even in the presence of advanced disease. Home treatment of DVT is safe and feasible and is likely to affect the quality of life of cancer patients positively. Further randomized controlled studies comparing in-hospital treatment and home treatment of DVT may be warranted.

WA and PSW were the major contributors to this work and were primarily responsible for it, from conception to submitted manuscript. All authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibility for the following parts of the content: RG, SL, FD, and LS collection of clinical data; LS had also a role in designing the study, interpreting the data and preparing the article.

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