Journal of Thrombosis and Haemostasis, **2**: 1311–1315

ORIGINAL ARTICLE

Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study

M. MONREAL,* L. ZACHARSKI,† J. A. JIMÉNEZ,‡ J. RONCALES§ and B. VILASECA¶

**Servicio de Medicina Interna, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; †Dartmouth Medical School, Lebanon, New Hampshire and the VA Hospital, White River Jct., Vermont, USA; ‡Servicio de Radiodiagnóstico, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; §Servicio de Hematología, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ¶Servicio de Medicina Interna, Hospital Universitari Germans Trias i Pujol, Badalona, Spain*

To cite this article: Monreal M, Zacharski L, Jiménez JA, Roncales J, Vilaseca B. Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study. *J Thromb Haemost* 2004; **2**: 1311–5.

Summary. *Introduction*: Secondary prevention of venous thromboembolism (VTE) with vitamin K antagonists is often problematic in patients with cancer. We prospectively evaluated the effectiveness and safety of long-term subcutaneous dalteparin in a series of consecutive patients with symptomatic VTE and metastatic cancer. *Patients and Methods*: The study included 203 patients, aged 36–96 years. The initial treatment consisted of a 7-day course of subcutaneous dalteparin according to body weight. Then, patients received a fixed dose of 10 000 IU dalteparin once daily for at least 3 months. In patients developing transient thrombocytopenia the dose was reduced to 5000 IU daily while the platelet count remained <50 000; and to 2500 IU daily while it remained <10 000. Patients undergoing any surgical intervention during the study were put on 5000 IU daily during the first 4 days, switching thereafter to 10 000 IU. Patients undergoing any other invasive procedure (i.e. biopsies, punctures) received a 5000 IU dose the same day, instead of 10 000 IU. *Results*: Eleven patients (5.4%) developed major bleeding complications (6 fatal) during the 3-month study period, and 18 patients (8.9%) developed VTE recurrences (2 patients died). There were no higher complication rates in patients with either liver or brain metastases, nor during thrombocytopenia, surgery or invasive procedures. *Conclusions*: Fixed dose 10 000 IU subcutaneous dalteparin once daily for 3 months was not associated with more complications in patients with liver or brain metastases. The dose adjustment for patients with thrombocytopenia, surgery or invasive procedures was safe too.

Correspondence: Professor M. Monreal, Hospital Universitari Germans Trias i Pujol, 08916 Badalona, Barcelona, Spain.
Tel.: +34 93 465 1200; fax: +34 93 3952229; e-mail: mmonreal@ns.hugtip.scs.es

Received 21 January 2004, accepted 31 March 2004

Keywords: cancer, low-molecular-weight heparin, venous thromboembolism.

Introduction

Secondary prevention of venous thromboembolism (VTE) with vitamin K antagonists is often problematic in patients with metastatic cancer. Many of them have either liver or brain metastases, thus increasing the risk for bleeding complications. In addition, the need for frequent blood sampling to adjust the dose, and the need for temporary cessation of therapy to accommodate chemotherapy-induced thrombocytopenia and invasive procedures may also be inconvenient in severely ill patients. Recent studies have shown that low molecular weight heparins (LMWH) may be a good alternative to vitamin K antagonists since they do not require laboratory monitoring and may provide more flexibility and stability of coverage to accommodate thrombocytopenia and invasive procedures [1,2].

In a previous trial we found long-term treatment with fixed-dose 5000 IU dalteparin twice daily to be a good alternative in patients with VTE and contraindications to vitamin K antagonists [3]. In a latter, prospective cohort study with a large series of patients with VTE 10 000 IU dalteparin once daily was as effective and safe as coumarin [4]. In the present study we evaluated the effectiveness and safety of the same dose dalteparin in a series of consecutive patients with VTE and disseminated cancer.

Patients and methods

This prospective cohort study included consecutive patients with metastatic cancer and either symptomatic deep venous thrombosis (DVT) in the lower limbs or pulmonary embolism (PE) attended at the Hospital Universitari Germans Trias i Pujol, Badalona, Spain. The study was carried out in accord-

ance with the principles of the Helsinki–Tokyo declaration. Prior to commencing the trial, the necessary approvals were obtained from the Ethics Committee of the Hospital. Eligible patients were provided with an information sheet, and oral consent was obtained.

Patients

Patients with an acute episode of symptomatic DVT of the lower limbs were included if confirmed by either bilateral ascending venography or real-time B-mode compression ultrasound. Patients with suspected PE were included if the diagnosis was confirmed by ventilation-perfusion lung scan. Confirmation was pursued in patients with either high – or indeterminate -probability lung scans and confirmed DVT in the lower limbs. Recruitment of patients began in January 1996 and ended in March 2003.

Anticoagulant therapy

The initial treatment consisted of a 7-day course of subcutaneous dalteparin (Fragmin®, Pharmacia, Sweden) according to body weight, as previously reported [5]. Then, patients received a fixed dose, 10 000 IU dalteparin once daily for at least 3 months. Platelet count was measured at least once monthly during the study period. In all patients developing major bleeding complications LMWH doses were transiently withheld or reduced. Patients with recurrent DVT were put on 12 500 IU of LMWH, while a filter in the inferior vena cava (without increase in LMWH dosage) was inserted in those who developed recurrent PE.

In patients developing transient thrombocytopenia the LMWH dose was reduced to 5000 IU daily while the platelet count remained below 50 000; and to 2500 IU daily while it remained below 10 000. Patients undergoing any surgical intervention during the study were put on 5000 IU daily during the first 4 postoperative days, switching thereafter to 10 000 IU. Finally, patients undergoing any other invasive procedure (i.e. biopsies, punctures) received a 5000 IU dose the same day, instead of 10 000 IU.

Outcomes

After discharge all patients were followed-up in our outpatient clinic at 1-month intervals during the first 3 months. At each visit special attention was paid to any sign or symptom suggesting either DVT or PE recurrences, or bleeding complications. Each episode of clinically suspected recurrent DVT or PE was documented by repeat CUS, venography or lung scanning. Bleeding complications were classified as major or minor according to the criteria by Doyle *et al.* [6]: bleeding was classified as major if it was clinically overt and was either associated with a decrease in the hemoglobin level of 2.0 g dL^{-1} or more, led to a transfusion of 2 units of blood or more, or was retroperitoneal or intracranial. Bleeding was defined as minor if it was overt but did not meet the criteria for major bleeding.

Statistical analysis

The significance of a number of clinical variables for the risk of either major bleeding or VTE recurrence was tested by fitting bivariate proportional hazards models. Proportions and their exact 95% confidence intervals were calculated (Confidence Interval Analysis, version 2.0.0).

Results

During the study period a total of 237 consecutive patients were diagnosed with acute VTE and disseminated cancer. Of these, 34 patients did not enter the study for the following reasons: 14 patients major bleeding during initial therapy, four due to massive or recurrent PE; five due to death for other reasons; and 11 patients due to LMWH therapy at lower doses than usual (due to abnormal coagulation tests). Therefore, the study included 203 patients (71 females and 132 males) aged 36–96 years (mean age, 65). Of these, 146 (72%) had acute DVT and 57 had PE. The most common sites of cancer were the lung, 58 patients; colon, 24; prostate, 22; breast, 15; stomach, 13; and carcinoma of unknown origin, 13 patients. The clinical characteristics are depicted in Table 1.

No patient was lost to follow-up. One hundred and fifty-seven patients (77%) received chemotherapy. Fifty-five patients (27%) developed transient thrombocytopenia (<100 000 platelets mm^{-3}) during the 3-month study period. In 33 patients the platelet count decreased below 50 000. Thrombocytopenia was attributed to chemotherapy in 49 patients, and to malignancy in five. Twenty patients (10%) needed surgery during the study period: in eight patients tumor excision; in four intestinal obstruction; in two hip fracture; in six other reasons. Furthermore, 27 patients (13%) underwent the following invasive procedures: seven paracenthesis; seven open biopsy; four thoracocentesis; four needle-guided biopsy; three port-system insertion; and two arthrocenthesis. Sixty-four patients (32%) died during the study period due to causes non-related to either PE or bleeding.

Eleven patients (5.4%) developed major bleeding complications (6 fatal) during the 3-month study period: five patients had gastrointestinal bleeding; two had gross hematuria; two large hematoma; one brain; one wound bleeding. Three patients with fatal bleeding were in a terminal condition, two further patients had a serum creatinine level over 3 times the upper limit of the normal range. Three patients with major bleeding developed acute PE shortly after either reduction or transient discontinuation of LMWH therapy. Sixteen further patients (7.9%) developed minor bleeding complications (7 patients hematuria; 5 epistaxis; 4 other sites). No major bleeding (but 7 minor) events appeared in patients with transient thrombocytopenia. No bleeding events were seen shortly after invasive procedures or surgery. Major bleeding

Table 1 Descriptive statistics of the 203 patients according to cancer site

	GI $n = 38$	GU $n = 56$	Breast $n = 15$	Lung $n = 58$	Others $n = 36$
Clinical characteristics					
Gender (males)	66%	62%	0	86%	61%
Age, mean (years)	64 ± 10	69 ± 11	70 ± 10	60 ± 10	64 ± 13
Age, range (years)	42–83	39–88	47–84	42–85	36–96
Body weight (kg)	68 ± 12	70 ± 14	67 ± 12	68 ± 10	68 ± 12
VTE characteristics					
Proximal DVT	95%	82%	80%	86%	92%
Pulmonary embolism	32%	20%	33%	34%	25%
Risk factors					
Postoperative	18%	16%	13%	19%	8%
Bedrest	18%	21%	20%	22%	33%
VTE history	16%	13%	27%	10%	8%
Cancer characteristics					
Time since diagnosis (mo.)	18 ± 22	28 ± 31	79 ± 32	10 ± 12	10 ± 11
Lung metastases	32%	30%	47%	28%	39%
Liver metastases	53%	29%	13%	10%	47%
Brain metastases	13%	7%	7%	59%	17%
Bone metastases	21%	54%	47%	26%	25%
Treatment of cancer					
Chemotherapy	74%	84%	93%	83%	56%
Thrombocytopenia	26%	27%	20%	34%	19%
Need for surgery	16%	11%	13%	5%	8%
Invasive procedures	18%	9%	7%	10%	22%
Clinical events					
Minor bleeding	5%	14%	13%	6%	3%
Major bleeding	11%	9%	0	2%	3%
Recurrent VTE	16%	9%	0	7%	8%
Death	39%	34%	20%	31%	47%

GI = gastrointestinal; GU = genitourinary; VTE = venous thromboembolism; DVT = deep venous thrombosis.

complications were significantly more common in females, but they were not more frequent in patients with either liver or brain metastases (Table 2).

Besides the three patients whose VTE recurred shortly after modifying LMWH therapy due to major bleeding, 18 further patients (8.9%) developed VTE recurrences during the study period. There were 10 cases of symptomatic DVT (6 of which were in the contralateral limb) and eight patients with PE (2 of which died shortly after the PE). No significant correlation was found between recurrent VTE and any clinical variables (Table 2). No recurrences developed shortly after invasive procedures or surgery, nor during LMWH dose adjustments in patients with transient thrombocytopenia.

Discussion

Secondary prevention of VTE with vitamin K antagonists is often problematic in patients with metastatic cancer. Achieving the target INR is especially problematical due to a high background risk of drug interactions, malnutrition, vomiting, and liver dysfunction. Accordingly, they usually require more regular monitoring of the prothrombin time than non-cancer patients. This is particularly difficult since they frequently have limited and difficult venous access or are geographically distant from their oncologist. Moreover, due to its delayed onset of action and slow clearance, interruption of warfarin treatment is required several days before invasive procedures, and therapeutic levels may not be reached again for some days after the procedure is completed. Apart from the theoretical reduction in thromboembolic protection during these periods, the interruptions further complicate the difficulties of dose adjustment. Thus, in clinical practice many physicians are reluctant to use long-term warfarin therapy in the setting of significant thrombocytopenia, cerebral metastases or active bleeding [7,8]. Although scant data are available to justify these concerns, anecdotal case reports and series suggest that warfarin therapy is probably sufficiently hazardous that other alternatives should be considered for patients with VTE under these conditions.

A number of trials compared LMWHs with oral anticoagulants in the long-term prevention of VTE [9–14]. These were of short duration and included primarily patients without cancer, but a recent meta-analysis [15] showed a statistically non-significant reduction in the rate of VTE recurrences and major bleeding complications in favor of LMWH. The recently published CLOT study, conducted in a large cancer population, has demonstrated that dalteparin can be used for the long-term management of VTE, resulting in significantly reduced rates of recurrent VTE in comparison with standard oral anticoagulation with warfarin, without any increase in bleeding [2]. Previous to CLOT, the study by Meyer *et al.* also

Table 2 Univariate analysis of the risk for developing major bleeding complications and VTE recurrences

Variables	Frequency (%)	Major bleeding ($n = 11$)	Recurrent VTE ($n = 18$)
Clinical characteristics			
Gender (females)	33%	9.4 (1.8–65.3)	0.7 (0.2–2.3)
Age >65 years	50%	0.5 (0.1–2.1)	0.7 (0.3–2.1)
Body weight >69 kg	50%	0.3 (0.1–1.3)	0.8 (0.3–2.4)
VTE characteristics			
Proximal DVT	86%	0.4 (0.1–1.9)	2.7 (0.3–56)
Pulmonary embolism	27%	1.5 (0.4–6.0)	1.3 (0.4–4.1)
Risk factors for VTE			
Postoperative	14%	2.1 (0.4–9.5)	1.1 (0.2–4.5)
Immobility	22%	3.0 (0.7–11.8)	0.6 (0.1–2.5)
Previous VTE	13%	0.7 (0.03–5.5)	0.9 (0.1–4.4)
Cancer site			
Gastrointestinal	19%	2.7 (0.6–10.9)	2.4 (0.7–7.8)
Genitourinary	28%	2.2 (0.6–8.5)	1.0 (0.3–3.1)
Breast	7%	0.0 (0.0–6.2)	0.0 (0.0–3.4)
Lung	29%	0.2 (0.0–1.9)	0.7 (0.2–2.4)
Others	18%	0.5 (0.0–3.4)	1.0 (0.2–3.9)
Metastases			
Lung	33%	2.6 (0.7–10.5)	1.4 (0.5–4.2)
Liver	29%	0.9 (0.2–3.8)	1.2 (0.4–3.8)
Brain	22%	0.7 (0.1–3.5)	0.4 (0.1–1.7)
Bone	34%	0.7 (0.1–3.1)	1.6 (0.5–4.7)
Events during the study period			
Chemotherapy	77%	0.3 (0.1–1.3)	1.5 (0.4–7.0)
Thrombocytopenia	27%	1.0 (0.2–4.4)	0.8 (0.2–2.6)
Need for surgery	10%	0.9 (0.4–7.6)	1.2 (0.2–6.3)
Invasive procedures	13%	0.6 (0.1–5.2)	1.3 (0.3–5.4)

VTE = venous thromboembolism; DVT = deep venous thrombosis.

demonstrated that LMWH may be a good alternative to antivitamin K drugs [1].

Ours is the first prospective study including consecutive patients with acute VTE receiving long-term treatment with LMWH. Thus, it should be considered more reflective of standard clinical practice than randomised clinical trials: 34% of the evaluable patients in the CLOT trial, and over 50% in the Meyer *et al*. trial were not included, the most common reasons being either chemotherapy known to induce thrombocytopenia, inability to reach the clinical center easily, or a poor ECOG score [1,2]. Furthermore, also at variance with the above mentioned trials, all patients in our series had metastatic cancer. Both bleeding complications and thromboembolic recurrences are much more common in patients with metastases [16]. Also at variance with the two previous clinical trials the LMWH dose regimen used in our study was not based on body weight. In this way, any conclusions have to be drawn cautiously, but we failed to find any association between body weight and either major bleeding or VTE recurrences.

Twenty-seven per cent of our patients developed transient thrombocytopenia, mostly related to chemotherapy, 10% had to be operated and 13% underwent invasive procedures during the 3-month study period. First, we demonstrated that 10 000 UI dalteparin once daily is not associated to higher complication rates in patients with either liver or brain metastases. Second, the LMWH-dose adjustments in patients with thrombocytopenia, surgery or invasive procedures again were not associated to higher complication rates.

References

1 Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, Le Maignan C, Extra JM, Cottu P, Farge D. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer. *Arch Intern Med* 2002; **162**: 1729–35.

2 Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Math M, Haley S, Kovacs MJ, Gent M. Low-molecular-weigh heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **34**: 146–53.

3 Monreal M, Lafoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. *Thromb Haemost* 1994; **71**: 7–11.

4 Monreal M, Roncalés FJ, Ruíz J, Muchart J, Fraile M, Costa J, Hernández JA. Secondary prevention of venous thromboembolism: a role for low-molecular-weight heparin. *Haemostasis* 1998; **28**: 236–43.

5 Monreal M, Büller H, Lensing AWA, Bonet M, Roncales J, Muchart J, Fraile M. Should patients with deep venous thrombosis alone be treated as those with concomitant asymptomatic pulmonary embolism? A prospective study. *Thromb Haemost* 2002; **88**: 938–42.

6 Doyle J, Turpie AG, Hirsh J, Best C, Kinch D, Levine MN, Gent M. Adjusted subcutaneous heparin or continuous intravenous heparin in patients with acute deep vein thrombosis. *Ann Intern Med* 1987; **107**: 441–5.

7 Vucic N, Ostojic R, Svircic T. Treatment of deep vein thrombosis with oral anticoagulants in patients with malignancy: prospective cohort study. *Croat Med J* 2002; **43**: 296–300.
8 Streiff MB. Vena cava filters: a comprehensive review. *Blood* 2000; **95**: 3669–77.
9 Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, Tagliaferri A, Dettori AG. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. *Thromb Haemost* 1994; **72**: 191–7.
10 Das SK, Cohen AT, Edmonson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. *World J Surg* 1996; **20**: 521–7.
11 Lopaciuk S, Bielska-Falda H, Noszczyk W, Bielawiec M, Witkiewicz W, Filipecki S, Michalak J, Ciesielski L, Mackiewicz Z, Czestochowska E, Zawilska K, Cencora A. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost* 1999; **81**: 26–31.
12 Gonzalez-Fajardo J, Arreba W, Castrodeza J, Perez JL, Fernández L, Agundez I, Mateo AM, Carrera S, Gutiérrez V, Vaquero C. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep vein thrombosis. *J Vasc Surg* 1999; **30**: 283–92.
13 Veiga F, Escriba A, Maluenda M, Lopez Rubio R, Margalet I, Lezana A, Gallego J, Ribera JM. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep vein thrombosis in the elderly: a randomized trial. *Thromb Haemost* 2000; **84**: 559–64.
14 Hull R, Pineo G, Mah AF. Long-term low molecular weight heparin treatment versus oral anticoagulant therapy for proximal deep vein thrombosis. *Blood* 2000; **96**: 449a.
15 Iorio A, Guercini F, Pini M. Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. *J Thromb Haemost* 2003; **1**: 1906–13.
16 Prandoni P, Lensing AWA, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; **100**: 3484–8.