Support Care Cancer (2008) 16:847–852
DOI 10.1007/s00520-007-0339-3

ORIGINAL ARTICLE

Prophylactic anti-coagulation in cancer palliative care: a prospective randomised study

Catherine Weber · Thierry Merminod · François R. Herrmann · Gilbert B. Zulian

Received: 17 July 2007 / Accepted: 18 September 2007 / Published online: 17 October 2007

Abstract
Goals The objective of this study was to determine utility of prophylactic anti-coagulation in cancer patients hospitalised for palliative care in a specialised centre.
Materials and methods Prospective 1:1 open randomised study was designed. Twenty patients aged 55 to 88 years with advanced cancer and an estimated life expectancy of less than 6 months were assigned to either receive treatment with 2,850/3,800 U (<70/>70 kg) of daily subcutaneous nadroparin or no treatment. Suspicion of venous thrombo-embolism (deep vein thrombosis and pulmonary embolism) was confirmed by echo-Doppler examination of the lower limbs and/or by spiral computed tomography scan of the lungs. Bleeding episodes were recorded. Platelet count was measured on days 7 and 14. Survival time from study entry was determined.
Main results One venous thrombo-embolism and one major bleeding occurred in the group receiving nadroparin, whereas two minor bleedings occurred in the control group. At 3 months, nine of ten participants had died in the control group vs five of ten in the group receiving nadroparin (P=0.141). Five participants could be discharged home (P=0.141).
Conclusions Decision to administer prophylactic nadroparin in hospitalised cancer patients under palliative care remains a challenge. Better mobility score at admission and the likelihood to be discharged home may be useful for practical purposes. The observation of a potential influence of prophylactic nadroparin on survival deserves further studies.

C. Weber · T. Merminod · F. R. Herrmann · G. B. Zulian (✉)
Department of Rehabilitation and Geriatrics, Service of Palliative Medicine Cesco, University Hospitals of Geneva,
11 chemin de la Savonnière,
1245 Collonge-Bellerive, Switzerland
e-mail: gilbert.zulian@hcuge.ch

Keywords Anti-coagulation · Cancer · Palliative care · Thrombosis · Bleeding

Introduction

The association between cancer and venous thrombo-embolic disease (VTE) was first described by Trousseau 140 years ago [26]. Cancer type and extension can facilitate VTE together with other risk factors such as bed confinement, anti-cancer treatments, central venous devices and advanced age [2, 6, 9, 10, 12, 19, 25, 27]. Prevalence of VTE in cancer patients hospitalised for palliative care can be estimated at 10% [22].

Low molecular weight heparin (LMWH) is the standard treatment for the prevention of VTE during the first weeks after surgery, during immobilization of the lower limb and during acute hospitalisation for congestive heart failure, respiratory insufficiency, infection, rheumatology problems or inflammatory bowel disease [20, 24]. LMWH therapy has also been shown to increase survival of patients with advanced malignancies and a life expectancy superior to 6 months [15, 17].

In palliative care for cancer patients, primary prophylaxis of VTE has not been proven useful despite the presence of many risk factors in most patients. Decision to administer VTE prophylaxis may thus depend on health professional experience, place of care and patients' preferences [14]. Widely prescribed in acute hospitals, VTE prophylaxis is rarely administered in nursing homes and even less frequently at home, although risk factors are not different for this patient population.

The main objective of palliative care is to improve patients' quality of their remaining lifetime [3, 28]. In this context, prophylactic treatments may also be justified because anticipation of problems is one key to achieve this

goal. Such treatments should virtually have no side effects and should decrease the risk of unpleasant complications while avoiding futile investigations. This is the reason why we started the present open prospective randomised study.

Materials and methods

The study was approved by the Ethic and Research Committee of University Hospitals of Geneva. Consecutive cancer patients admitted to the centre of continuous care with an estimated life expectancy inferior to 6 months were eligible. Objectives were to determine the occurrence of VTE, to detect complications and to measure survival time from study entry.

Exclusion criteria

Patients with absence of judgement abilities precluding to sign written informed consent, VTE during the past 6 months, active bleeding, creatinine clearance <20 ml/min, thrombocytopenia <50 G/l, past history of heparin thrombocytopenia, partial thromboplastin time (PTT) >45 s, prothrombin time (TP) <35% and concomitant anti-coagulation treatment on admission were excluded form this study.

Randomisation procedure

Patients were randomised 1:1 with the heparin group receiving LMWH and the control group receiving neither LMWH nor placebo. Sets of 20 sealed envelopes were prepared by one of us (FH) and numbered consecutively. Each envelope contained one YES (LMWH prophylaxis) or NO (no prophylaxis). The sequence of treatments was randomly assigned in blocks of constant size (n=20). There were 10 YES and 10 NO in each block. Envelopes were opened by the principal investigator (CW) to allow treatment allocation.

Treatment

Nadroparine (Fraxiparine®) was provided by the University Hospitals of Geneva central pharmacy. Dose was 0.3 ml, i.e. 2,850 U of anti-Xa factor for patients <70 kg and 0.4 ml, i.e. 3,800 U of anti-Xa factor for patients >70 kg. Nadroparine was administered once daily as a subcutaneous injection.

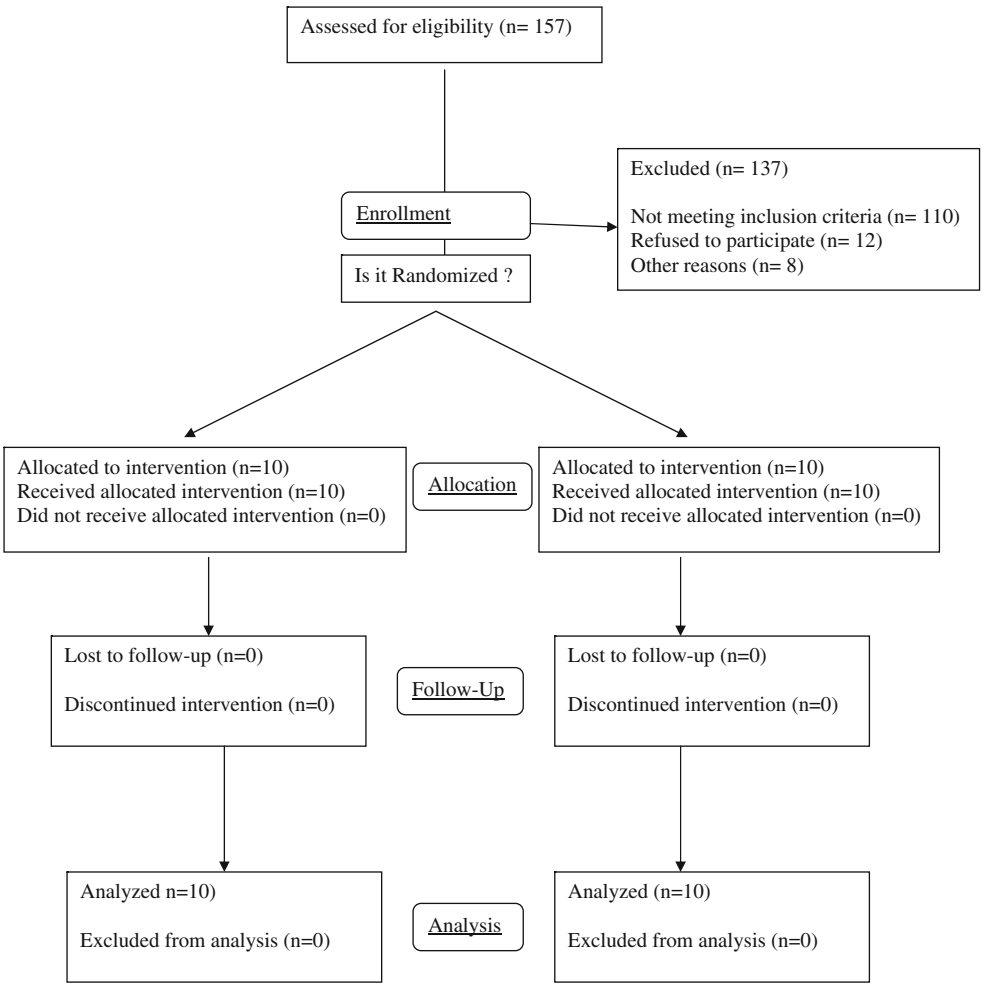

Fig. 1 The Consort E-Flowchart

Table 1 Treatment allocation, tumour characteristics and outcome

Number	Group	Age	Gender	Cancer	Histology	Metastasis	Outcome
1	Control	79	M	Head and neck	Squamous cell	Lymph nodes	Death
2	LMWH	69	F	Chronic lymphocytic leukaemia		Lymph nodes	Home
3	Control	71	F	Breast	Adeno-carcinoma	Liver, bone	Death
4	Control	65	M	Head and neck	Squamous cell	Bone	Death
5	Control	74	F	Breast	Adeno-carcinoma	Liver, bone	Death
6	LMWH	78	F	Rectum	Adeno-carcinoma	Liver, lung, peritoneum	Death
7	LMWH	88	F	Lung	Squamous cell	Lung	Home
8	LMWH	63	F	Breast	Adeno-carcinoma	Liver, bone, lung	Home
9	LMWH	84	M	Lung	Adeno-carcinoma	Lung	Home
10	Control	81	F	Pancreas	Adeno-carcinoma	Liver	Death
11	LMWH	67	M	Rectum	Adeno-carcinoma	Liver	Death
12	LMWH	55	M	Stomach	Adeno-carcinoma	Liver	Death
13	Control	79	M	Head and neck lung	Squamous cell	Brain	Death
14	Control	61	F	Lung	Small cell	Brain, liver, lung	Death
15	LMWH	84	F	Ovary	Adeno-carcinoma	Peritoneum	Death
16	LMWH	56	F	Pancreas	Adeno-carcinoma	Lung	Death
17	LMWH	83	M	Stomach	Adeno-carcinoma	Liver	Home
18	Control	67	M	Lung	Squamous cell	Brain	Home
19	Control	64	F	Breast	Adeno-carcinoma	Brain	Death
20	Control	57	M	Bladder	Transitional cell	Liver	Death

Additional tests

Clinical suspicion of deep vein thrombosis (DVT) indicated the necessity for an echo-Doppler examination of the lower limbs. Clinical suspicion of pulmonary embolism (PE) also indicated the necessity for such test; if negative for DVT, a spiral computed tomography (CT) scan was then requested. Platelet count was controlled on days 7 and 14 to screen for heparin-induced thrombocytopenia. Bleeding episodes were recorded and blood controls made accordingly.

Table 2 Participants' general characteristics

	Total[a] (N=20)	Nadroparin[a] (N=10)	Control[a] (N=10)	P value[b]
Age (years)	70.0	73.5	69.0	0.520
Gender M/F	10/10	4/6	5/5	1.000
Weight (kg)	63.9	62.4	67.8	0.384
TP (%)	90.5	88	91	0.544
PTT (s)	28.1	28,1	28.1	0.744
Platelets (G/l)	234	210	248	0.450
Creatinine (μmol/l)	80	89	73	0.910
Creatinine clearance (ml/min)	56	55	59	0.910
Duration of cancer disease (months)	18	30	12.5	0.075
WHO performance status	2.5	2	3	0.029
Functional Independence Measure (FIM) score (max 126)	123	124	122	0.331
Mini Mental State (MMS) score (max 30)	28	28	29	0.517

[a] Median for continuous variables and number (%) for non-continuous variables
[b] P calculated with Fisher's exact test for non-continuous values and Mann–Whitney U test for continuous values

Statistical analysis

A two-group continuity corrected chi-square test with a 0.050 two-sided significance level would have 80% power to detect a difference between a group 1 proportion of 0.0500 and a group 2 proportion of 0.0125 (odds ratio of 0.241) when the sample size in each group would reach 389. After 18 months, only 20 subjects could be enrolled among 157 eligible patients. We thus decided to analyse the results and to submit them for publication.

Table 3 Events recorded during the study

	Total[a] (N=20)	Nadroparin[a] (N=10)	Control[a] (N=10)	P value[b]
DVT or PE	1 (5)	1 (10)	0 (0)	1.000
Minor bleeding	2 (10)	0 (0)	2 (20)	0.474
Major bleeding	1 (5)	1 (10)	0 (0)	1.000
Death	14 (70)	5 (50)	9 (90)	0.141

[a] Number (%)
[b] P calculated with Fisher's exact test
DVT Deep venous thrombosis, *PE* pulmonary embolism

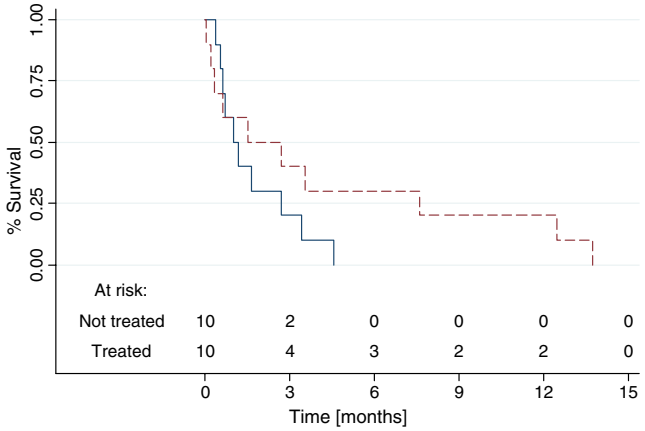

Fig. 2 Kaplan–Meier survival curves according to treatment status (*dotted line*, treated with nadroparin; *solid line*, not treated). Log-rank test, P=0.2382. N=20

As a pilot, this study provides the number needed to perform adequate power analysis. Comparisons between groups were made with Fischer's exact test for binary variables and with Mann–Whitney's test for ordinal or continuous variables. A survival analysis was performed using the Kaplan–Meier life-table method. Curves were compared using a log-rank test. Analyses were done with Stata version 9.2 software (Stata Corporation 2005, College Station, TX, USA). Survival data was obtained from the central state population registry [7].

Results

Twenty patients were included over a period of 18 months. This represented 13% of the total population of cancer patients admitted for palliative care to our 104-bed hospital with an estimated life expectancy of less than 6 months (Fig. 1). Low accrual was explained by LMWH contraindication, patients' incompetence to sign informed consent and patients' refusal to participate in the study.

Patients' characteristics

Age varied between 55 and 88 years with a median of 69 years in the control group and of 73.5 years in the group receiving prophylactic nadroparin, but this was not statistically different. There was only one haematology tumour and 19 solid tumours, and all were far advanced and/or widely metastasised cancers. Most were adeno-carcinomas, eight in the nadroparin group and four in the control group. Duration of cancer disease before admission was 30 months in the nadroparin group and 12.5 months in the control group (P=0.075). Mini Mental State [8] and Functional Independence Measure [16] scores were comparable. However, WHO performance status was 3 in the control group and 2 in the group receiving prophylactic nadroparin, and this was statistically different (P=0.029; Tables 1 and 2).

Events

VTE occurred once as both DVT and PE at the same time in a patient receiving prophylactic nadroparin. Major bleeding occurred once as a rectorrhagia in a patient receiving prophylactic nadroparin, and two patients of the control group presented minor bleeding with sputum and diarrhoea (Table 3). No episodes of thrombocytopenia were recorded either on days 7 and 14 as per protocol or later during the clinical course. Six patients (33%) could be discharged home with five of them in the group receiving prophylactic nadroparin, but the difference was not significant.

At 3 months, there was a tendency towards more deaths in the control group with nine patients dying, whereas five died in the group receiving prophylactic nadroparin (P= 0.141). Two patients survived for more than 9 months in the treated group vs 0 in the other group.

The Kaplan–Meier survival curves are shown in Fig. 2, but there was no statistical difference between the groups according to the log-rank test (P=0.2382).

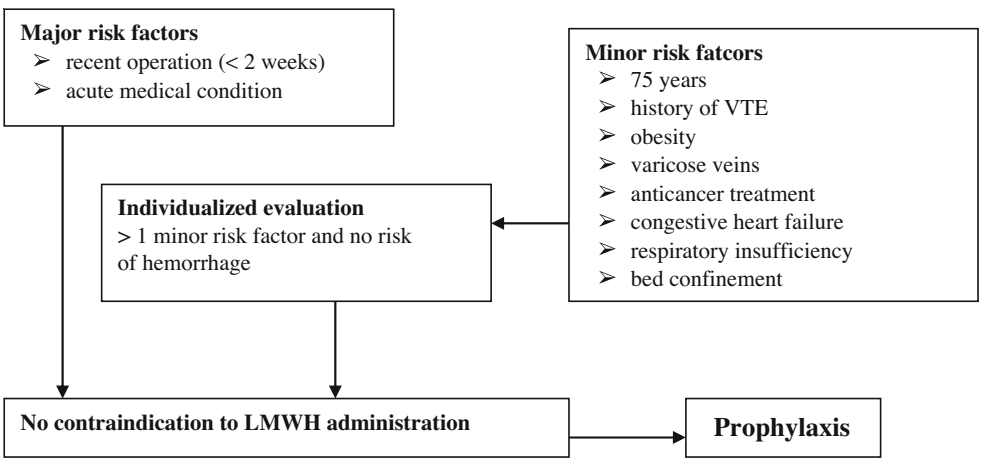

Fig. 3 Proposition of a decisional algorithm for prophylactic LMWH administration in the presence of risk factors for VTE in cancer patients under palliative care

Post hoc power analysis reveals that a Fisher's exact test with a 0.050 two-sided significance level will have 81 and 90% power to detect the difference between a treated group proportion of 0.500 and a control group proportion of 0.900 when the sample size in each group reaches 23 and 29 subjects, respectively.

Discussion

Utility of prophylactic anti-coagulation in palliative care has yet to be demonstrated. The results of our open prospective randomised study did show neither clear benefit for the administration of prophylactic nadroparin nor obvious disadvantages.

More deaths occurred in the control group during the study and may have resulted from undetected VTE. Terminal VTE might thus have occurred, but this hypothesis couldn't be verified because autopsy was not performed.

Patients receiving prophylactic nadroparin had a statistically significant better WHO performance status at inclusion, and 50% of them could be discharged home. Duration of cancer was longer and there were more adenocarcinomas in the nadroparin group, but the difference did not reach statistical significance. Taken together though, these factors may suggest a more indolent course of the disease explaining why a higher level of activity was retained. In addition, mobility, as an indication of both physical and psychological well-being, may be a good protection factor against VTE. We would thus encourage physical exercise in patients capable and willing to maintain activity during the palliative phase of cancer.

Our study included a limited number of patients despite large inclusion criteria confirming the technical difficulties of specific palliative-care research [1, 4, 5, 11, 18, 21]. Inability to give informed consent because of poor general conditions at admission was the main reason for participants' exclusion. Given the recruitment difficulties encountered in our specialised palliative care centre, we would call for the design of multi-institutional collaborative studies to follow on this important subject. Alternatively, palliative-care cancer patients should have earlier access to this research as this may help obtain informed consent at a better time. Finally, the development of supportive care leading towards smoother transition from curative to palliative care may also be an appropriate answer to increase scientific research in favour of this highly vulnerable group of patients.

Practical guidelines based on other types of patients will thus continue to influence the prescription of prophylactic anticoagulation. In this respect, we would like to remind that hospitalisation by itself is not an indication for prophylactic LMWH, whereas immediate post-surgical period and acute medical problems are [13].

It would thus appear legitimate to prescribe prophylactic LMWH when patients' quality of life is good enough to indicate therapeutic anticoagulation in the case of a VTE event (Fig. 3). When life expectancy is a matter of days or perhaps even weeks, prophylactic anticoagulation is probably futile since most symptoms can be adequately controlled with other means [4, 14]

Palliative care faces great challenges in front of cancer augmentation and aging of the population [23, 29]. On the one hand, our study would suggest absence of a clear demonstration that the administration of prophylactic LMWH is of benefit for advanced cancer patients hospitalised for palliative care. There was, though, a tendency towards less death occurrence during hospitalization, and two participants survived beyond expectation. Previous results have suggested increase survival for cancer patients with a life expectancy of more than 6 months who received LMWH [17]. Our finding may thus contribute to extend LMWH administration to advanced cancer patients with the shortest life expectancy to facilitate home discharge and optimise the utilisation of health resources.

References

1. Agrawal M, Danis M (2002) End-of-life care for terminally ill participants in clinical research. J Palliat Med 5:729–737
2. Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M (1998) Venous thromboembolism and cancer. Lancet 351:1077–1080
3. Bruera E, Neumann CM (1998) Management of specific symptom complexes in patients receiving palliative care. Can Med Assoc J 158:1717–1726
4. Bruera E, Miller L, McCallion J, Macmillan J et al (1992) Cognitive failure in patients with terminal cancer: a prospective study. J Pain Symptom Manage 7:192–195
5. Casarett DJ, Karlawish JHT (2000) Are special ethical guidelines needed for palliative care research? J Pain Symptom Manage 20:130–139
6. Deitcher SR, Gomes MP (2004) The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. Cancer 101:439–449
7. Federal Office of Statistics (Switzerland). http://www.bfs.admin.ch/
8. Folstein MF, Folstein SE, Mc Hugh PR (1975) Mini-Mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
9. Goodnough LT, Saito H, Manni A, Jones PK, Pearson OH (1984) Increased incidence of thromboembolism in stage IV breast cancer patients treated with a five-drug chemotherapy regimen. A study of 159 patients. Cancer 54:1264–1268
10. Gouin-Thibaut I, Samama MM (2000) Venous thrombosis and cancer. Ann Biol Clin (Paris) 58:675–682
11. Hawryluck L (2004) People at the end of life are a vulnerable research population. Clin Oncol 16:225–226
12. Jacobs LG (2003) Prophylactic anticoagulation for venous thromboembolic disease in geriatric patients. J Am Geriatr Soc 51:1472–1478
13. Jilma B, Kamath S, Lip GYH (2003) Antithrombotic therapy in special circumstances. II-in children, thrombophilia, and miscellanaous conditions. Br Med J 326:93–96

14. Johnson MJ, Sherry K (1997) How do palliative physicians manage venous thromboembolism? Palliat Med 11:462–468
15. Kakkar AK, Levine MN, Kadziola Z et al (2004) Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: The Fragmin Advanced malignancy Outcome Study (FAMOUS). J Clin Oncol 22:1944–1948
16. Keith RA, Granger CV, Hamilton BB, Sherwin FS (1987) The functional independence measure: a new tool for rehabilitation. Adv Clin Rehabil 1:6–18
17. Klerk CPW, Smorenburg SM, Otten HM et al (2005) The effect of low molecular weight heparin on survival in patients with advanced malignancy. J Clin Oncol 23:2130–2135
18. Koedoot CG, de Haan RJ, Stiggelbout AM et al (2003) Palliative chemotherapy or best supportive care? A prospective study explaining patients' preference and choice. Br J Cancer 89:2219–2226
19. Lee AYY (2003) Epidemiology and management of venous thromboembolism in patients with cancer. Thromb Res 110:167–172
20. Leizorovicz A, Cohen AT, Turpie AGG et al (2004) Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 110:874–879
21. Mazzocato C, Sweeney C, Bruera E (2001) Clinical research in palliative care: choice of trial design. Palliat Med 15:261–264
22. Merminod T, Zulian GB (2007) Venous thromboembolism in cancer patients under palliative care: retrospective study with lessons to the future. Supportive Palliative Cancer Care J (in press)
23. Pautex S, Moynier K, Weber C, Zulian GB (2002) L'évaluation des symptômes en oncologie palliative. Méd Hyg 60:1313–1317
24. Samama MM, Cohen AT, Darmon JY et al (1999) A comparaison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. New Eng J Med 341:793–800
25. Saphner T, Tormey DC, Gray R (1991) Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol 9:286–294
26. Trousseau A (1865) Phlegmasia Alba Dolens. Clinique médicale de l'Hôtel Dieu de Paris, vol 3. The New Sydenham Society, London, p 94
27. Wilson CB, Lambert HE, Scott RD (1987) Subclavian and axillary vein thrombosis following radiotherapy for carcinoma of the breast. Clin Radiol 38:95–96
28. World Heath Organization. http://www.who.int/cancer/palliative/definition/en/
29. Yancik R (2005) Population aging and cancer: a cross-national concern. Cancer 11:437–441