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ORIGINAL ARTICLE

Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study

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Abstract
Purpose Whether an anticoagulant prophylaxis is needed for patients with cancer with a central venous catheter is a highly controversial subject. We designed a study to compare different prophylactic strategies over 3 months of treatment.
Methods We performed a phase III prospective, open-label randomized trial. After the insertion of a central venous access device, consecutive patients with planned chemotherapy for cancer were randomized to no anticoagulant prophylaxis, low molecular weight heparin [low molecular weight heparin (LMWH); with isocoagulation doses], or warfarin 1 mg/day. Treatments were given over the first 3 months. Doppler ultrasound and venographies were performed on days 1 and 90, respectively, or sooner in case of clinical presumption of thrombosis.
Results A total of 420 patients were randomized, and 407 were evaluable. Forty-two catheter-related deep vein thrombosis (DVT) occurred (10.3 %), 20 in those with no anticoagulation, 8 in those receiving warfarin, and 14 in those receiving LMWH. Nine additional non-related catheter deep vein thrombosis (CDVT) occurred. Anticoagulation significantly reduced the incidence of catheter-related DVT ($p = 0.035$) and catheter non-related DVT ($p = 0.007$), with no difference between warfarin and LMWH. Safety was good (3.4 % of attributable events) but compliance with randomized prophylaxis was lower than expected.
Conclusions Prophylaxis showed a benefit regarding catheter-related and non-catheter-related DVT with no increase in serious side effects.

Keywords Cancer · Catheter-related thromboembolism · Prophylaxis · LMWH

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Introduction

The risk of deep vein thrombosis (DVT) is more important in patients with cancer than in the general population because of their prothrombotic state. Central venous access devices (CVAD) are commonly implanted for the administration of chemotherapy, but are also associated with a high rate of DVT, which are known to be an important risk factor for morbidity and *de facto* lead to a significant increase in deaths [1–3].

Thromboprophylaxis for catheter-associated thrombosis remains then a real challenge.

The exact incidence of upper-limb thromboses in patients with a CVAD is difficult to quantify. The incidence ranges from 0.3 to 28.3 % in symptomatic patients and from 27 to 66 % when asymptomatic DVT are included [4–6]. There are several pro-thrombotic factors such as cancer-related hypercoagulability, vessel injury during insertion [4–6], location of the catheter [6–8], erythropoiesis-stimulating agent use, platelet count $>350 \times 10^9$/l, and previous hemorrhage [6, 9, 10].

When this study was designed, there were only few consensus statements concerning the impact of thromboprophylaxis in ambulatory cancer patients. We conducted a prospective randomized trial to assess the efficacy of prophylactic antithrombotic treatment [low molecular weight heparin (LMWH) or warfarin] versus control to prevent DVT in high-risk ambulatory patients with locally advanced or metastatic solid tumor, with a CVAD. We estimated the frequency of both symptomatic and asymptomatic DVT of the upper limbs and cervical veins in patients receiving prophylactic anticoagulants compared with patients with no prophylaxis.

Patients and methods

Study patients

Four hundred and twenty consecutive patients were enrolled from September 1999 through June 2009 in the centre hospitalier universitaire (CHU) de Limoges. The inclusion criteria were as follows: (1) histological evidence of solid invasive cancer, locally advanced or metastatic status; (2) presence of a subclavian central venous catheter inserted for less than 7 days; (3) starting a first line of chemotherapy; (4) aged 18 years or older; (5) life expectancy of more than 3 months; (6) performance status between 0 and 2 (ambulatory); (7) platelets greater than 100×10^9/l and normal activated partial thromboplastin time (aPTT); and (8) the capacity to provide informed consent.

Exclusion criteria were as follows: (1) renal or hepatic failure (creatinine clearance <20 ml/min); (2) acute infectious disease; (3) history of an allergic reaction to warfarin or heparin, or of thrombocytopenia due to heparin; (4) uncontrolled high blood pressure; (5) ongoing hemorrhagic syndrome; (6) concomitant disease which recommended heparin treatment; (7) formal indication for warfarin or antiplatelets agents in preventive or curative doses; (8) pregnant or breast-feeding woman; (9) recent history of DVT in the past 6 months; (10) presence of cerebral metastasis; and (11) previous CVAD in the past year.

Central venous access devices were subcutaneously implanted by experimented practitioners in surgical units. The tip position was checked by X-ray.

The study protocol was approved by the local ethical committee.

Study design and treatment plan

This was a phase III, open-label, randomized trial. Eligible patients were randomized to receive oral warfarin (1 mg/day), subcutaneous LMWH at recommended doses for prevention (dalteparine, nadroparine, or enoxaparine, once daily), or no prophylaxis. In each arm, the allocated treatment started in the first 6 days after CVAD implantation and was prescribed for 90 days. Doses were not adjusted.

On day (D)1 and D90, a systematic Doppler ultrasound (US) of the upper limbs and cervical veins coupled with venography by CVAD injection was performed, or sooner if local symptoms of DVT appeared. Thrombocytopenia and coagulation disorders were evaluated at baseline, and then before each chemotherapy cycle (i.e., every 3 or 4 weeks), a clinical examination was also performed.

An additional platelet count was performed for patients in the LMWH arm on D5, D8, D11, D14, and D17.

Endpoint measures

The primary outcome measure was the rate of symptomatic and asymptomatic catheter-related DVT of the ipsilateral upper limbs and cervical veins, without or with prophylaxis with either LMWH or warfarin. Superior vena cava, subclavian vein, jugular and humeral vein thrombosis, and pulmonary embolisms of unknown origin were recorded; intraluminal or localized thrombi inside the implantable device were not considered.

Symptoms suggestive of thrombosis included pain, edema, or erythema located on the CVAD vein territory or symptoms of pulmonary embolism. Asymptomatic DVT were blindly assessed by both Doppler US and venographies. Secondary endpoints were the benefit from either LMWH or low-dose warfarin and the rate of symptomatic venous thromboembolic events in other venous territories.

Statistical considerations

The primary endpoint and qualitative variables were compared between the groups using chi-square test or Fisher's exact test, if appropriate. Continuous variables were compared using Student's test or Mann–Whitney test, as appropriate. A p value of less than 0.05 was considered to indicate statistical significance. The intention to treat

population was evaluated and was defined as all randomized patients. CONSORT revised guidelines were used.

The sample size was based on an incidence of DVT of 40 % in absence of prophylaxis versus 20 % in one of the 2 prophylaxis groups during the 3-month period [3]. Using an overall 5 % α risk and a 10 % β risk, 420 patients were required. The randomization list was generated by an independent statistician who used a standard method of permuted block of variable size without stratification. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, USA).

This study was registered at ClinicalTrials.gov, number NCT00199602.

Results

Patients

Between 1999 and 2009, 420 consecutive patients were included and provided informed consent. The patient characteristics are summarized in Table 1. The median age was 61 (range 21–85) years, and the sex ratio male/female was 1.5. Half the patient population had a primary inoperable tumor, and 191 patients (46 %) had a metastatic extension. All solid tumor localizations were represented. Multiple chemotherapy protocols were used, and no patient received antiangiogenic drugs.

Randomization allowed to include 137 patients in the no anticoagulation arm, 141 in the LMWH arm, and 135 in the warfarin arm (Fig. 1). Seven patients withdrew their consent or had no data, 6 were lost to follow-up, so 407 patients were evaluable for the main objective, well balanced.

Twenty-three deaths occurred during the 3-month follow-up (5.6 %) in the intention to treat population and were well balanced between the 3 arms, 8 in the no anticoagulation arm, 8 in the warfarin arm, and 7 in the LMWH arm.

The CVAD was implanted, using a non-invasive procedure, on the right side in 74 %. The access point was either the subclavian or internal jugular vein. The distal catheter tip location was checked by an initial chest X-ray, to control if it was situated at the junction between the right atrium and the superior vena cava, corresponding to an X-ray at vertebra level T5–T7 as recommended by standard recommendations (7): Twenty-two were situated higher than this level.

There was no difference between the three arms according to platelet and hemoglobin level, age, sex, body mass index (BMI), CVAD side repartition, or lower level of the distal extremity of the CVAD previous surgery. This item includes patients for whom it has been decided just before randomization to perform a surgery on primary tumor, nodes, or metastases.

DVT results

Global results

Fifty-one DVTs occurred in all territories (12.6 %). One patient experienced a fatal pulmonary embolism.

Catheter-related deep vein thromboembolism (CRDVT)

Forty-two patients developed a CRDVT in the ipsilateral upper-limb territory (10.3 %); 20 occurred in the 135 patient control arm group, 22 in 272 patient anticoagulation group (8 warfarin, 14 in LMWH arm) (Table 2). There was a significant benefit for use of a preventive anticoagulation treatment ($p = 0.0357$). The relative risk of thrombosis was 0.55 with a 95 % confidence interval (CI) between 0.31 and 0.96. There was no difference between warfarin and LMWH treatment toward CRVTE ($p = 0.20$). The mean delay of occurrence of CRDVT was 50 days, and 30 were asymptomatic (71 %). Five of the asymptomatic cases were diagnosed on D1 (3 by Doppler US and 2 by venography) and 15 on D90 (5 by Doppler US and 10 by venography). Two patients were diagnosed by chance during surgery performed for the cancer resection (head and neck cancers), and 2 others thanks to a computed tomography scan planned for tumor evaluation. The other 6 asymptomatic thromboses were discovered during venography or Doppler US, which was performed between D8 and D68 (protocol deviation or isolated CVAD dysfunction situations).

Half CRDVT localization was at the distal extremity of the catheter, in the superior vena cava and half in the subclavian vein with regards to the site of puncture, with an extension in the proximal or distal venous network in 7 cases. Whereas Doppler US was the most frequently used examination for diagnosing subclavian and cervical thrombosis (81 % of them), venography was better for those in the superior vena cava (95 %).

Factors associated with CRDVT

Age, sex, CVAD side, baseline platelet level $\geq 350.10^9$/l, hemoglobin level <10 g/dl, Body Mass Index ≥35, use of erythropoiesis agents, previous hemorrhage, previous surgery, and concomitant parenteral nutrition did not influence the incidence of CRDVT (Table 3).

There was a relationship between the immediate absence of blood at the CVAD aspiration and CRDVT ($p < 0.0001$). In our study, we confirmed that a too high catheter tip level was associated with CRDVT ($p = 0.009$ in Fisher's test, relative risk = 3.03, 95 % CI 1.5–6.1).

Table 1 Baseline demographic and tumor characteristics of the study population ($n = 407$)

Characteristics	Control ($n = 135$)	Warfarin ($n = 134$)	LMWH ($n = 138$)	p value
Age, years				
Mean (minimum–maximum)	60 (21–85)	59 (24–81)	61	0.16
Standard deviation (SD)	11.8	10.9	10.6	
Médian	61	60	63	
Interquartile range (IQR)	17.7	14	14	
Sex				
Males	84	81	78	0.62
Females	51	53	60	
Cancer primary localization				
Head and neck	34	30	32	0.85
Breast	16	16	11	0.47
Lung or pleura	16	16	13	0.75
Colorectal and anal	19	20	21	0.92
Esophagus and stomach	20	20	24	0.80
Other digestive	0	2	1	0.35
Pancreas and biliary tract	6	8	6	0.78
Urinary (kidney and tract)	7	11	14	0.30
Pelvic gynecological	6	3	10	0.14
Other	5	4	5	0.93
Primary unknown	8	5	4	0.43
Baseline platelets count				
Mean (10^9/l)	261	221	201	
Median	234	241	237	
IQR	319	253	260	0.49
$\geq 350 \times 10^9$/l	42	53	49	0.058
Baseline mean hemoglobin level (g/dl)	12.25	12.73	12.29	0.64
Median	12.9	12.8	12.6	
IQR	2.4	2.4	2.4	
≤ 10	4	8	14	0.255
Previous surgery[a]	39	36	30	0.39
Distal catheter tip location				
In front of T5–T7	102	101	106	0.95
Higher than T5	7	7	8	0.96
Lower than T7	19	19	24	0.68
Unknown	9	8	3	0.18
Catheter access point				
Right subclavian	96	97	111	0.25
Left subclavian	39	38	30	
Unknown	1	0	0	

[a] On primary, nodes, or metastasis

Non-related catheter deep vein thrombosis (non-related CDVT) and arterial embolisms.

Nine additional non-related CDVT occurred. The locations of these events were inferior limb phlebitis (6 cases), contralateral upper limb and cervical vein thromboses (3 events). Eight of these were symptomatic, and all were objectively-confirmed.

Anticoagulation use also had an impact on non-related CDVT ($p = 0.007$ by Fisher's test on these 9 events; relative risk = 0.14, 95 % CI 0.03–0.67) with no difference between warfarin and LMWH use (0.75 versus 0.72 % of non-related CDVT, $p = 1$).

Two arterial thromboses occurred (2 myocardial infarctions) in the control group.

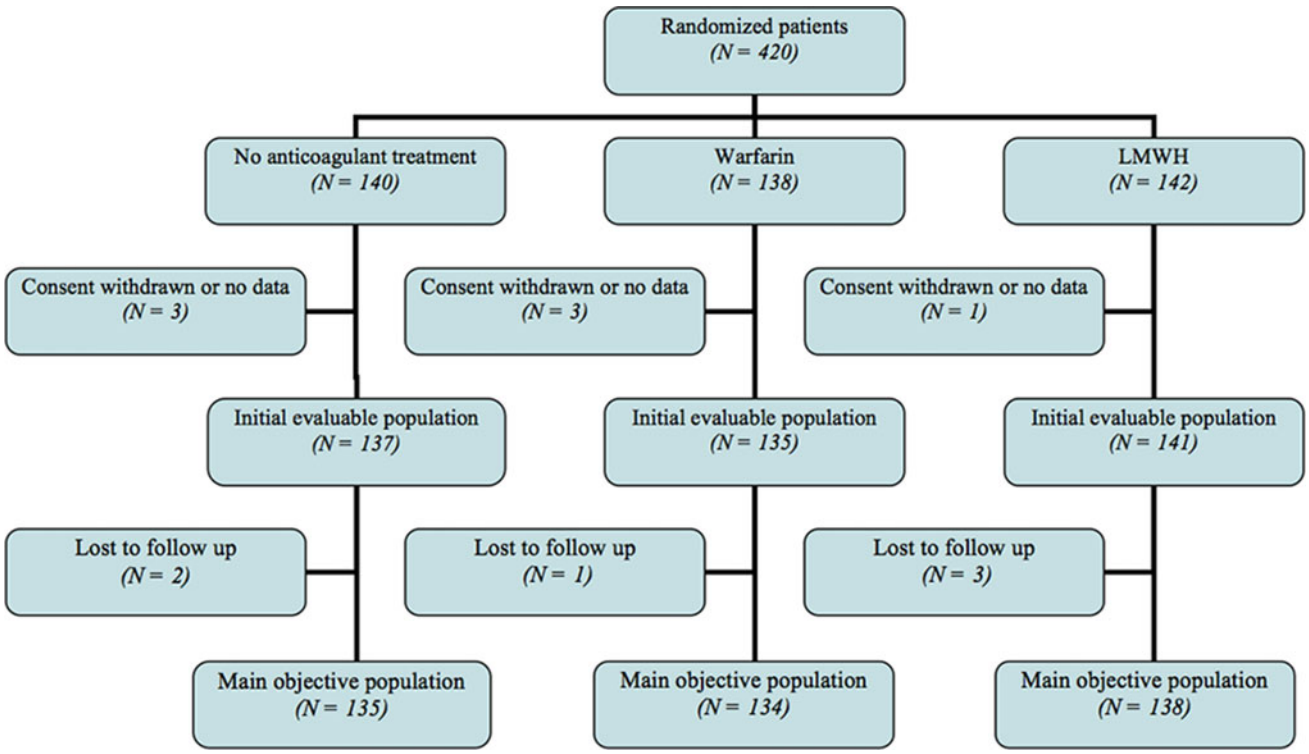

Fig. 1 CONSORT diagram

When both non-related CDVT and CRDVT are considered, the difference remains significant with efficiency of a prophylactic anticoagulant ($p = 0.001$).

Safety and treatment-related toxicity

Twenty-seven toxicity events, with the exception of thrombosis and infections, were attributed to the prophylactic treatment, CVAD insertion, or to the mandated examinations. Ten minor bleeds or biological coagulation marker modifications occurred (nosebleeds, PTT decreases, tumor bleed, rectorrhagia, and hematomas), with no death. There was no increase in bleeding in patients receiving anticoagulants ($p = 0.33$).

Twenty-three patients (5.6 %) experienced thrombocytopenia grade 3 or 4 (National Cancer Institute common terminology criteria V 3.0). Whatever the grade, 53 cases of thrombocytopenia occurred in the no anticoagulant arm, 34 in the warfarin arm, and 59 in the LMWH arm. The thrombocytopenia was mainly chemotherapy-induced, but was increased with anticoagulant use ($p < 0.0001$), mainly with LMWH ($p = 0.002$).

Two specific allergies to warfarin were reported, and 3 renal failures occurred, in the LMWH arm. Of interest, no drug interaction was reported.

Central venous access device-related adverse events included 4 pneumothorax, one extravasation during venography, and 7 CVAD removals because of a bad insertion.

Feasibility and compliance

In all arms, one-third of patients did not follow their allocated treatment until D90 (Table 4).

The mean delay for discontinuation is 37 (range 1–82) days, with no difference between the allocated treatments. These discontinuations were due to DVT, toxicity, introduction of anticoagulation in the control arm, refusal of the patient, prescription error, or underlying disease. Of all patients, 3.5 % refused the allocated treatment and most were in the LMWH arm (9 patients).

Discussion

Our study shows that anticoagulants have significant efficiency in the prevention of CRDVT and global DVT in ambulatory cancer patients with a CVAD for chemotherapy. Several clinical trials of thromboprophylaxis have already been performed in heterogeneous cancer outpatient populations with conflicting results. Some studies found no benefit with LMWH [11–13] or warfarin [14–16], whereas others showed positive results with them [17, 18, 19–21]. In recent studies and meta-analyses, results are still contradictory [1, 2, 22–25].

The current guidelines of the American and European Societies [26–28] do not recommend prophylactic anticoagulant treatment for cancer outpatients. Of note, our study

Table 2 Description of the DVT population according to study arms ($n = 407$)

Events	Control ($n = 135$)	Warfarin ($n = 134$)	LMWH ($n = 138$)	All patients ($n = 407$)
Median Age (range), years	61 (42–78)	59 (40–73)	63 (44–74)	61 (40–78)
Sex (males/females)	14/6	4/4	9/5	27/15
DVT, catheter-related, *n*	20	8	14	42
Localization of DVT,[a] *n*				
Superior vena cava	10	5	6	21
Subclavian	6	1	4	11
Internal jugular	4	1	3	8
Axillary and/or humeral	3	2	1	6
Cephalic	1	0	1	2
Pulmonary embolism with no etiological local DVT	1	0	0	1
Symptomatic thrombosis	9	0	3	12
Mean delay (days)	45	56	53	50
Method of diagnosis				
Venography	10	4	4	18
US Doppler	8	3	8	19
DVT, non-catheter-related, *n*	7	1	1	9
Localization of DVT,[a] *n*				
Inferior limbs	4	1	1	6
Contralateral internal jugular	2	0	0	2
Cephalic	1	0	0	1
Symptomatic thrombosis	6	1	1	8
Mean delay (days)	45	56	53	50
Method of diagnosis				
US Doppler	7	1	1	9

DVT deep vein thrombosis, *US* ultrasound

[a] Several localizations may have been found on the same exam

was started before they were published. Study enrollment was slow as the trial was initially planned as a multicenter trial but finally became a single center study.

The incidence of CVAD-related DVT in cancer patients varies considerably [4–6, 25]. However, with 15.6 % thrombosis, the overall number of thromboembolic events (catheter and non catheter-related) was low in this trial, as observed in some prospective trials [17, 29].

Seventy one percent of CRDVT were asymptomatic: They are important to detect because they can be associated with pulmonary embolism [1–4, 6, 24] or loss of functioning of the CVAD, preventing the continuation of chemotherapy.

Safety was good with both anticoagulant treatments in our study, our rate of bleeding is not as high as previously reported [1, 24]. Moreover, only 23 cases of thrombocytopenia grade 3 or 4 occurred, higher in the anticoagulation arms: This event sometimes makes us stop the anticoagulation, although anticoagulation's causality could not be formally identified during chemotherapy's regimen.

In our study, 72 % of patients received the allocated treatment for all 3 months of the study, but many concomitant events might have interfered with it over the 3-month period. The anticoagulation treatment period should be reevaluated, and a shorter course considered [30].

Day 90 Doppler US and venographies were not always performed to detect asymptomatic thrombosis [4, 25, 31]. Causes are numerous, but mostly, the scheduled time slots were not available in the departments.

Finally, we cannot recommend the routine use of these examinations in DVT detection, as they should be reserved for clinical trials.

This study suggests that the use of prophylactic anticoagulant treatment can prevent symptomatic and asymptomatic thromboses in ambulatory cancer patients at high risk for DVT and with long-term central lines for chemotherapy. Our results do not distinguish between warfarin and LMWH in terms of efficacy.

Khorana high-risk factors [9, 32, 33]. have not been highlighted in our study, but patients' population had not

Table 3 Risk factors for CRDVT; univariate analysis ($n = 407$)

Factors	Non-thrombosis patients ($n = 365$)	CRDVT patients ($n = 42$)	p value
Median age (years)	60	61.5	0.4
Sex			
Male	220	23	0.49
Female	145	19	
Side of CVAD			0.28
Left	93	14	
Right	270	28	
Inferior level of CVAD tip			0.028
≤T4 (chest radiology)	17	7	
>T4	329	35	
BMI (kg/m2)			0.24
<35	356	40	
≥35	7	2	
Concomitant use of CVAD for intravenous nutrition			0.92
Yes	53	6	
No	304	36	
Baseline platelets			0.052
$<350 \times 10^9$/l	242	22	
$\geq 350 \times 10^9$/l	117	20	
Baseline mean hemoglobin level (g/dl)			0.74
≤10	23	3	
>10	336	39	
Tumor response			0.25
Partial or complete response	111	9	
Stable or progressive disease	136	18	
High-risk or very high-risk tumor localization (Khorana score)			0.43
Yes	117	16	
No	248	26	
Possibility of blood aspiration by CVAD at baseline			0.2
Yes	363	41	
No	2	1	
Possibility of blood aspiration by CVAD at the end of study[b]			<0.0001
Yes	269	21	
No	13	11	
Concomitant erythropoiesis agents			0.89
Yes	45	5	
No	312	37	
Previous hemorrhage in last 6 months			1.0
Yes	4	0	
No	341	40	0.75
Previous surgery[a]			
Yes	95	10	
No	270	32	

CVAD central venous access device, *CRDVT* catheter-related deep vein thromboembolism

[a] On primary, nodes, or metastasis

[b] Which is the day of thrombosis in CRDVT patients

been designed according to these criteria in 1999. As a recent study showed that new ultra-LMWH could reduce the incidence of thromboembolic events too [34], additional studies should be performed with new drugs [35], using Khorana high-risk scale for a better determination of patients for whom a benefit or prophylaxis should be expected.

Table 4 Etiologies of premature discontinuations from allocated treatment ($n = 407$)

Events	Control ($n = 135$)	Warfarin ($n = 134$)	LMWH ($n = 138$)	All arms ($n = 407$)
Treatment discontinued (3 months), *n* (%)	34 (25)	36 (27)	45 (33)	115 (28)
Mean delay for discontinuation (days)	37 (1–82)	36 (1–81)	38 (1–82)	37 (1–82)
Reason for discontinuation				
Toxicity[a]	0	6	5	11 (10 %)
Concomitant event[b]	15	20	20	55 (48 %)
Non-compliance[c]	2	3	9	14 (12 %)
Protocol deviation[d]	0	4	8	12 (10 %)
Thrombosis event(veinous or arterial)	17	3	3	23 (20 %)

[a] Considered to be related to the allocated treatment

[b] Concomitant event that forbade the allocated treatment, including death

[c] Non-compliance (refusal) of the patient or lost to follow-up

[d] Protocol deviation including prescription error or general practitioner decision

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Conflict of interest None.

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