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Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial

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Background: Cancer patients receiving chemotherapy experience thromboembolic complications associated with the use of long-term indwelling central venous catheters (CVCs). This prospective, double-blind, placebo-controlled, multicenter study evaluated whether prophylactic treatment with a low molecular weight heparin could prevent clinically relevant catheter-related thrombosis.

Patients and methods: Patients with cancer undergoing chemotherapy for at least 12 weeks (n = 439) were randomly assigned, in a 2:1 ratio, to receive either dalteparin (5000 IU) or placebo, by subcutaneous injection, once daily for 16 weeks. Patients underwent upper extremity evaluation with either venography or ultrasound at the time of a suspected catheter-related complication (CRC) or upon completion of study medication. The primary end point, as determined by a blinded adjudication committee, was the occurrence of a CRC, defined as the first occurrence of any one of the following: clinically relevant catheter-related thrombosis that was symptomatic or that required anticoagulant or fibrinolytic therapy; catheter-related clinically relevant pulmonary embolism; or catheter obstruction requiring catheter removal.

Results: There was no significant difference in the frequency of CRCs between the dalteparin arm (3.7%) and the placebo arm (3.4%; P = 0.88), corresponding to a relative risk of 1.0883 (95% confidence interval 0.37–3.19). No difference in the time to CRC was observed between the two arms (P = 0.83). There was no significant difference between the dalteparin and placebo groups in terms of major bleeding (1 versus 0) or overall safety.

Conclusions: Dalteparin prophylaxis did not reduce the frequency of thromboembolic complications after CVC implantation in cancer patients. Dalteparin was demonstrated to be safe over 16 weeks of treatment in these patients.

Key words: cancer therapy, catheter-related complication, prophylaxis, venous thrombosis

introduction

Thromboembolic complications occur commonly in cancer patients. The pathogenesis is multifactorial, including a release of procoagulants by tumor cells and anticancer drugs. This association between cancer and thromboembolic disease has been recognized for over a century [1]. Recent advances in biochemistry, cell biology and molecular biology have helped to provide a better understanding of the complex interactions between tumor cells and the hemostatic system [2]. In addition to the procoagulant properties of tumor cells, many treatment interventions for patients with cancer, including surgery, chemotherapy and hormonal therapy are known to increase the risk of venous thromboembolism [3].

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The use of central venous catheters (CVCs) is well established for the delivery of cytotoxic agents, blood components or parenteral nutrition in patients with cancer. However, an increased risk of thromboembolic complications associated with long-term, indwelling CVCs have been recognized as a serious problem, leading to significant morbidity, catheter malfunction and treatment delays [4, 5]. While the majority of catheter-related complications (CRCs) are related to the local effects of catheter thrombosis (clinical signs and symptoms of upper limp thrombosis, malfunctioning catheter), pulmonary embolism has been reported to occur in ~5–12% of patients [6–8].

The incidence of catheter-related thrombosis (CRT) reported in studies conducted in cancer patients is highly variable. Some studies have reported frequencies ranging from 37% to 66%, while other studies have described lower rates ranging from 4% to 13% [4, 9–14]. Several reasons may account for these variations including variable definitions of CRT, methods of CRT assessment, heterogeneity of study population, and differences of the catheter in length, diameter and material.

The interpretation of published literature on prevention of CVC thrombosis and other CRCs is, however, limited by a relative lack of randomized trial data. In fact, only two randomized trials evaluating the role of anticoagulation in CVC thrombosis were published when this study started [10, 15].

In a trial conducted by Bern et al. [15], the administration of 1 mg warfarin as thromboprophylaxis in 40 cancer patients with CVC was examined versus 42 cancer patients who received no treatment. Warfarin significantly reduced the thrombotic event rate related to the CVC as compared with the control group (9.5% versus 37.5%).

Monreal et al. [10] randomized a total of 29 cancer patients to dalteparin administered at a dosage of 2500 IU once daily versus a control group without treatment. However, the study was stopped early owing to the high incidence of thrombosis in the control group of patients (eight out of 13 patients; 62%). In the dalteparin-treated group only one out of 16 patients developed CRT (6%).

Although these two trials suggested that anticoagulants might be beneficial in preventing CRTs, unequivocal conclusions could not be drawn from these small studies.

The current study is the first large multinational, double-blind, placebo-controlled, prospective study to evaluate the efficacy and safety of dalteparin in the prevention of clinically relevant or symptomatic CRT in patients with cancer receiving chemotherapy via CVCs.

patients and methods

end points

The primary end point was the occurrence of a CRC, defined as the first occurrence of any one of the following: clinically relevant CRT that was symptomatic or that required anticoagulant therapy or therapeutic infusion of a fibrinolytic agent with or without catheter removal; catheter-related clinically relevant pulmonary embolism with or without catheter removal; or catheter obstruction requiring catheter removal.

Secondary end points were: the incidence of CRCs per day of exposure to the study drug; the incidence of asymptomatic CRT not requiring any intervention during the study period; the time to the first clinically relevant CRC; the time to catheter removal; the use of bolus injections of fibrinolytic agents for CRT or catheter obstruction (with or without catheter removal); catheter-related infection (with or without catheter removal) or a positive catheter-tip culture; the incidence of clinically relevant and objectively verified non-catheter-related venous or arterial thromboembolic event (TEE); and clinical and laboratory adverse events.

study design

This study was a phase III, randomized, double-blind, prospective, placebo-controlled trial carried out in 48 different centers in the following countries; Austria, Canada, France, Germany, Greece, Portugal, the Russian Federation, the Slovak Republic, South Africa, Sweden, the UK and the USA. Consecutive eligible patients with documented cancer were randomly assigned, within 5–7 days of catheter placement, to receive either dalteparin (5000 IU) or placebo (0.2 ml saline), injected subcutaneously once daily. Patients were enrolled between August 1999 and June 2001. The randomization favored dalteparin at a 2:1 ratio. Patients were allocated to the treatment arm based on whether catheter insertion was proximal or distal to the axilla and by institutional site by centralized interactive voice processing system. Study medication continued for 16 weeks or until the occurrence of a CRC, catheter removal, a non-catheter-related thrombosis, death, an adverse event leading to cessation of treatment, other unacceptable toxicity, development of clinically relevant prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT). Catheter flushing with UFH (500 IU)/saline bolus flushes were allowed during catheter use. During periods of chemotherapy- or radiotherapy-induced thrombocytopenia, study medication was withheld until the platelet count rose to at least 30 000/mm^3.

All patients had assessments for primary and secondary end points at weeks 1, 2, 4, 8, 12 and 16. All patients underwent upper extremity evaluation [venography, ultrasound or computed tomography (CT) scan] upon the suspected occurrence of a CRC, removal of the catheter (planned or premature) or at 16 weeks from the start of study medication. Ventilation-perfusion (VQ) scan or spiral CT scan were used to verify pulmonary embolism occurrence. A central adjudication committee reviewed all venograms, CT scans, angiograms, compression ultrasonography examinations, VQ scans and other procedures obtained for a suspected CRC and made final judgement, blinded to patient treatment assignment.

Laboratory assessments of coagulation profile (PT, aPTT), complete blood count (hemoglobin, hematocrit, white blood cell count, absolute neutrophil count, platelet count) and chemistry profile [creatinine, aspartate aminotransferase (AST), total bilirubin, potassium] were performed. A major bleeding event was defined as a fall in hemoglobin of 2 g/dl or more or a 6% or greater reduction in hematocrit with manifest hemorrhage, any intraocular, intraspinal or intracranial hemorrhage, bleeding requiring blood transfusion, or fatal hemorrhage.

patients

Patients requirements for inclusion were as follows: histologically confirmed malignancy; placement of a CVC for chemotherapy within 5–7 days prior to randomization and treatment; an expected length of catheter use of at least 12 weeks; age ≥18 years; weight ≥40 kg; an Eastern Cooperative Oncology Group performance status of 0,1 or 2; a life expectancy of at least 16 weeks; adequate pretreatment organ function as demonstrated by a platelet count of at least 100 000/mm^3; an absolute neutrophil count of at least 1500/mm^3; total bilirubin and serum creatinine of up to 2× the upper limit of normal; AST up to 3× (patients without liver metastasis) or 5× (patients with liver metastasis) the upper limit of normal; and a PT/aPTT up to 1.5× the upper limit of normal. Positive local ethics

votes were obtained from all participating centers. All patients gave written informed consent to inclusion in the study.

Patients were excluded from the study for the following reasons: known hypersensitivity (including heparin-induced thrombocytopenia) to dalteparin, other low molecular weight heparins (LMWHs) or unfractionated heparin (UFH); active gastrointestinal or genitourinary tract bleeding; known coagulopathy; requirement for aspirin, dipyridamole, UFH, other LMWHs, warfarin or other anticoagulation therapy (heparin flushing allowed); active uncontrolled infection, including suspected catheter-related infection; known HIV positivity or AIDS-related illness; eye, ear or CNS surgery or a CNS trauma within the past 3 months; intracranial or intraocular hemorrhage (within 1 year) or retinal detachment (within 6 months); mental incapacitation or psychiatric illness that would prevent the provision of informed consent; uncontrolled hypertension, unstable angina, symptomatic congestive heart failure, myocardial infarction (within previous 6 months) or uncontrolled cardiac arrhythmia; severe concurrent disease; leukemia requiring induction/consolidation chemotherapy during the 16-week study period; requirement of high-dose chemotherapy and stem cell transplantation during the 16-week study period; use of investigational or unapproved catheter devices; and pregnancy, breastfeeding or likelihood of pregnancy.

statistics

The sample size was based on the assumption that the incidence of clinically significant CRCs would be 30% with placebo and 12% with dalteparin during the 16-week study period. To detect this reduction in CRC incidence in a two-sided comparison with alpha = 0.001, 80% power and a 2:1 randomization, a total of 435 patients would be sufficient, 290 patients in the dalteparin arm and 145 patients in the placebo arm. This calculation included a 15% increase in sample size to account for patients not adequately evaluable for the primary end point.

The primary end point was compared between the two treatment groups using the χ^2-test. Statistical testing on secondary end points was based only on two-sided Fisher's exact test. Intention-to-treat and as-treated study populations were evaluated.

results

patient characteristics

The patient characteristics are given in Table 1. Patients were well matched for age, gender, weight and race. Significantly more patients in the dalteparin arm had solid tumors (92.9%) compared with the placebo arm (86.2%; $P = 0.048$). The percentage of patients randomized but not receiving study medication was low and comparable in each arm (3.1% and 3.4% dalteparin and placebo, respectively). From 145 patients randomized to the placebo arm, 140 received at least one dose and from 294 patients randomized to the dalteparin arm, 285 received at least one dose. Early termination rates were comparable in each treatment arm. Of those treated, 67% and 67.1% in the dalteparin and placebo groups, respectively, completed the 16-week treatment. The reasons for early termination were similar in both treatment groups (Table 2). Adverse events, most related to the underlying cancer, withdrawal of consent and other reasons related to cancer accounted for ~80% of withdrawals. The majority of patients underwent an off-treatment evaluation of the catheter to detect asymtomatic thrombosis. End of treatment evaluation by venography was carried out in 61.3% ($n = 179$) and 59.3% ($n = 86$) of patients in the dalteparin and placebo treatment arms, respectively. In the remaining patients compression ultrasound was used for patency evaluation of the upper limp.

Table 1. Baseline characteristics of patients[a]

	Dalteparin	Placebo	*P*
Number of patients	294	145	
Age, years (mean ± SD)	55.2 ± 12.91	57.4 ± 12.72	0.10
Gender (% female)	59.2	57.2	0.70
Weight, kg (mean ± SD)	71.41 ± 15.41	70.73 ± 14.28	0.66
Race (% Caucasian)	94.6	93.8	0.87
Solid tumors (*n*)	271	125	0.048
Hematological tumors (*n*)	23	20	

[a]Intention-to-treat.
SD, standard deviation.

end point evaluations

The frequency of CRCs in the dalteparin arm was 3.7% compared with 3.4 in the placebo arm ($P = 0.88$), corresponding to a relative risk of 1.0883 [95% confidence interval (CI) 0.37–3.19; see Table 3]. In addition, there was no difference in the time to onset of CRC ($P = 0.83$) between patients on dalteparin or placebo (Figure 1). The overall event rate (3.6%) was substantially lower than the assumed rate used to calculate the sample size. The rate of CRCs was comparable between solid tumor patients and patients with hematological malignancies. Fifteen out of these 16 patients with CRCs had solid tumor diagnosis (CRC rate 3.8%) and one patient had a hematological tumor (CRC rate 2.3%).

The secondary end point analyses of non-catheter-related venous TEE and asymptomatic CRT are shown in Table 4. There were no significant differences in any of these events between the dalteparin and placebo group. Catheter-related infection data (including cases of positive catheter-tip culture) have been reported elsewhere [16].

safety data

The majority of patients had at least one adverse event. Most were due to non-study medication treatment or the underlying

Table 2. Reason for early withdrawal from the study[a]

	Dalteparin (*n* = 285) [*n* (%)[b]]	Placebo (*n* = 140) [*n* (%)[b]]
Adverse event	37 (39.4)	19 (41.3)
Protocol violation	1 (1.1)	1 (2.2)
Consent withdrawn	26 (27.7)	10 (21.7)
Lost to follow-up	0	2 (4.3)
Lack of efficacy	8 (8.5)	4 (8.7)
Catheter no longer needed	7 (7.4)	2 (4.3)
Death	4 (4.3)	1 (2.2)
Cancer-related reason	7 (7.4)	2 (4.3)
Investigator decision	2 (2.1)	0
Other	2 (2.1)	3 (6.5)
Total withdrawn	94 (100.0)	46 (100.0)

[a]As treated.
[b]Percent of withdrawals.

cancer. Overall, the adverse event profile was characteristic of an advanced cancer patient population.

Most of the reactions at the injection site occurred when dalteparin, and not placebo, was injected. These reactions consisted mainly of bruising (6.3% of patients), pain (2.8%) or hemorrhage (2.5%), but also edema, irritation and pruritus at the injection site (0.4% each). In only one patient skin ulceration was observed (0.4%). The proportion of patients who reported at least one of those reactions during the study was 9.5% with dalteparin and 2.9% with placebo. All the observed local reactions, however, were mild or moderate in severity (Table 5).

The frequency and analysis of bleeding is shown in Table 6. Bleeding events consisted of any type of hemorrhagic events including local events, such as hemorrhage or bruising at the injection site. The frequency of patients who had at least one hemorrhagic event during the study was comparable between the two arms (17.5% in the dalteparin group versus 15% in placebo-treated patients), corresponding to a relative risk of 1.20 (95% CI 0.69–2.10). Few of these events were of grade 3–4 and only two were described as major bleeding by the adjudication committee: one grade 4 gastric hemorrhage in the dalteparin arm and one grade 4 subarachnoid hemorrhage in the placebo arm.

Table 3. Frequency of CRC during study[a]

	Dalteparin (n = 294) [n (%)]	Placebo (n = 145) [n (%)]	P
Patients with CRC during study	11 (3.7)	5 (3.4)	0.88 OR 1.09 95% CI 0.37–3.19
Clinically relevant CRT	10 (90.9)	5 (100.0)	
Catheter-related clinically relevant pulmonary embolism	1 (9.1)	0	
Catheter obstruction requiring catheter removal	0	0	

[a]Intention-to-treat; adjudication committee's assessment.
CRC, catheter-related complication; OR, odds ratio; CI, confidence interval; CRT, catheter-related thrombosis.

discussion

The population entered in this phase III trial was recognized to be at high risk for thrombosis owing to the advanced stage of solid tumors in the majority of the patients, the placement of a CVC and the tumor treatment the patients were receiving [17–19].

Dalteparin administered 5000 IU subcutaneously once daily, a dose approved in many countries in high-risk patients undergoing surgical procedures [20], did not prove to be effective in reducing the frequency of CRCs in this study. Notably, the overall number of thromboembolic complications both catheter- and non-catheter-related that have been observed in this trial was unexpectedly low in both treatment arms.

The results of this trial are relevant. The strengths of this trial were a double-blind placebo-controlled study design, a the large sample size as well as a multinational recruitment of patients. The rate of CVC-related thrombosis reported in cancer patients is highly variable [21]. This may depend upon different patient populations as well the methodology used to assess the presence of a thrombus, and whether or not asymptomatic events were included [22–27]. However, rates of CRT in these studies were usually substanticially higher than demonstrated in our trial.

One possible explanation for the difference in the rate of thromboembolic complications between our trial and other studies is that many of the published trials were retrospective reviews. Some other trials were conducted in an open fashion, or were limited by a small number of patients included. In our trial, all the thrombotic events that could meet the criteria for the primary end point were reviewed in a blinded fashion by an independent adjudication committee. Under these strict trial conditions, the catheter-related thrombotic event rate was low and there was no difference between the two study arms. The

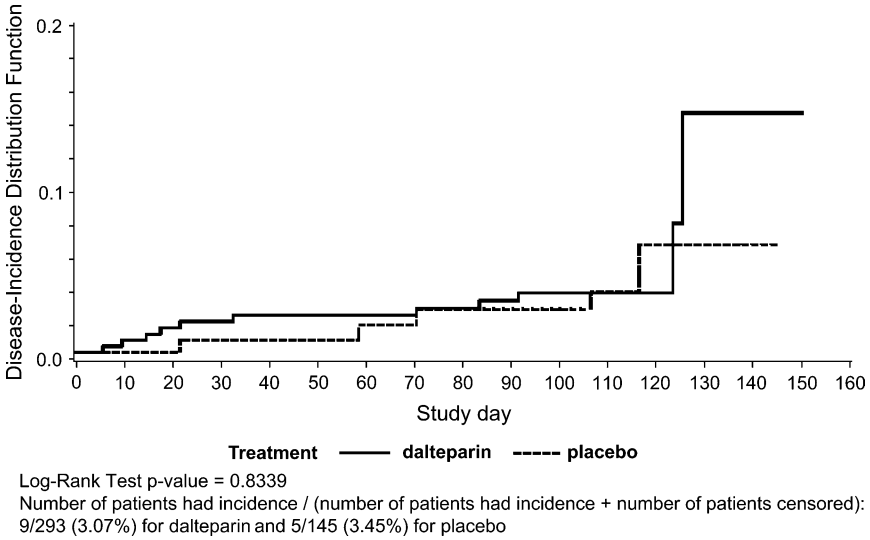

Figure 1. Time to catheter-related complication (intent to treat).

Table 4. Secondary end point analysis[a]

	Dalteparin (n = 294) [n (%)]	Placebo (n = 145) [n (%)]	P
Catheter-related infection[b]	11 (3.7)	6 (4.1)	NS OR 0.90 95% CI 0.32–2.49
Non-catheter-related venous TEE	3 (1.0)	1 (0.7)	NS OR 1.48 95% CI 0.15–14.4
Asymptomatic CRT	10 (3.4)	6 (4.1)	NS OR 0.81 95% CI 0.29–2.29

[a]Intention-to-treat.
[b]Includes patients reporting catheter-related infection and/or positive catheter tip culture.
NS, not significant; OR, odds ratio; CI, confidence interval; TEE, thromboembolic event; CRT, catheter-related thrombosis.

Table 5. Most common adverse events: system organ class analysis[a]

	Dalteparin (n = 285) [n (%)]	Placebo (n = 140) [n (%)]
Blood and lymphatic system disorder	88 (30.5)	33 (23.6)
Thrombocytopenia	17 (6.0)	9 (6.4)
Gastrointestinal disorders	180 (63.2)	90 (64.3)
Gastric hemorrhage	1 (0.4)	0
Gastrointestinal hemorrhage NOS	0	1 (0.7)
General disorders and administration site conditions	169 (59.3)	71 (50.7)
Injection site bruising	18 (6.3)	4 (2.9)
Injection site hemorrhage	8 (2.8)	0
Injection site pain	11 (3.9)	2 (1.4)
Infections and infestations	78 (27.4)	35 (25.0)
Nervous system disorders	70 (24.6)	37 (26.4)
Hemorrhagic stroke	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	79 (27.7)	28 (20.0)
Epistaxis	20 (7.0)	6 (4.3)
Hemoptysis	0	3 (2.1)
Skin and subcutaneous tissue disorders	79 (27.7)	38 (27.1)
Ecchymosis	13 (4.6)	6 (4.3)
Vascular disorders	35 (12.3)	18 (12.9)
Hematoma, NOS	3 (1.1)	3 (2.1)
Subarachnoid hemorrhage, NOS	0	1 (0.7)

[a]As treated.
NOS, not otherwise specified.

same results were observed with the secondary variables, i.e. the rate of asymptomatic CRTs, catheter-related infections and non-catheter-related TEEs. The rate of each variable in the placebo arm, however, was so low that meaningful differences could not be detected. Based on statistical design the study was underpowered to detect smaller differences. Therefore, it would now be necessary to have a much larger sample size for further trials.

In accordance with our results, Biffi et al. [27] reported a comparable incidence of CRT with a rate of 1.06% in cancer patients receiving LMWH as prophylaxis in a monocentric trial. Furthermore, very similar rates of catheter-related thrombosis were recently reported by Couban et al. [28], who investigated the prophylatic use of warfarin (1 mg daily fixed dose). In their randomized study, which included 255 patients, the frequency of symptomatic CVC-associated thrombosis in the placebo and coumadin arm was 4% and 4.6%, respectively. In another trial, Verso et al. [29] randomly assigned cancer patients scheduled for insertion of CVC to receive either subcutaneous enoxaparin 40 mg once a day or placebo. They started treatment 2 h before CVC insertion and continued for 6 weeks only. In this smaller study the rate of CRT was somewhat higher. Thus, deep venous thrombosis was observed in 22 patients (14.1%) treated with enoxaparin and in 28 patients (18%) treated with placebo, again without a significant difference between the two arms (P = 0.35). Taken together, in accordance to our study, all recently published randomized multicenter trials using LMWH or low-dose warfarin for prevention of venous thromboembolism associated with CVC failed to prove efficacy, as illustrated in Table 7. With respect to these data, anticoagulation is no longer recommended for routine prophylaxis of catheter-related thromboembolic complications in cancer patients [30].

Another concurrent explanation of the low rate of thromboembolic complications might be the type of the implanted catheter. In fact, most of the catheters placed in the present study were subcutaneous ports, which have been associated with fewer thrombotic events as compared with

Table 6. Frequency of bleeding: all events[a]

	Dalteparin (n = 285) [n (%)]	Placebo (n = 140) [n (%)]
Gastric hemorrhage	1 (0.4)	0
Gastrointestinal hemorrhage NOS	0	1 (0.7)
Hematemesis	1 (0.4)	0
Melena	1 (0.4)	0
Rectal bleeding	5 (1.8)	1 (0.7)
Injection site bruising	18 (6.3)	4 (2.9)
Injection site hemorrhage	8 (2.8)	0
Periorbital hemorrhage	0	1 (0.7)
Hematuria present	1 (0.4)	1 (0.7)
Hemorrhagic stroke	1 (0.4)	0
Menometrorrhagia	0	1 (0.7)
Vaginal hemorrhage	2 (0.7)	0
Epistaxis	20 (7.0)	6 (4.3)
Hemoptysis	0	3 (2.1)
Postoperative hemorrhage	1 (0.4)	1 (0.7)
Hematoma, NOS	3 (1.1)	3 (2.1)
Subarachnoid hemorrhage NOS	0	1 (0.7)
Total	50 (17.5)	21 (15.0)

[a]As treated.
NOS, not otherwise specified.

Table 7. Clinical trials for the prevention of central venous catheter (CVC)-related thrombosis

Study/Author	Design/*n* =	Verum and dosage	Duration of prophylaxis	Intervention/ Portflushing	Documentation of efficacy	Primary endpoint	Secondary endpoint	Bleeding episodes	Rate of CVC thrombosis
Bern et al. 1990 [15]	rd, op label, 90 pts	1 mg Warfarin 40 vs 42 pts no treatment	90 days, starting 3 days before insertion of CVC	Up to 500 IU heparin weekly	Venography at onset of symptoms or after 90 days	Thrombosis in the upper limp	Not available	Not available	4/42 (9.7%) warfarin vs 15/40 (37.5%) on placebo $P < 0.001$
Monreal et al. 1996 [10]	rd, mc, open label, 29 pts	Dalteparin 2500 IU or no treatment	90 days, starting 2 h before insertion of CVC	10 ml Heparinized saline solution	Venography at onset of symptoms or after 90 days	Thrombosis in the upper limp	Infection and major bleeding	1 Bleeding eps under dalteparin	1/16 (6%) dalteparin vs 8/13 (62%) control arm $P = 0.002$
Verso et al. 2005 [29]	db, rd, Italian trial, 11 centers $n = 385$	Enoxaparin 40 mg qd s.c. vs placebo, start 2 h before CVC insertion	6 weeks ± 2 days	No statement regarding use of port flushing	Ipsilateral upper limb venography (evaluable for efficacy in 310 of 385 pts)	Symptomatic + asymptomatic CVC-related thrombosis or PE or CVC removal. Ispsilateral venography, blinded review	Clinically ouvert TE events, deaths from TE or death from any cause during study or within 3 m of completion	No major bleeding complication	22/155 (14.1%) enoxaparin (2 symptomatic) 28/155 (18%) placebo (6 symptomatic) $P = 0.35$
Couban et al. 2005 [28]	rd, Canadian trial, 255 pts, 3 centers	Warfarin 1 mg p.o. vs placebo po	8 wks warfarin or 9 wks placebo, start within 72 h after CVC insertion, 196 interruptions of >7 d due to low PLT or INR>2	No statement; ass 100 mg, heparin in SCT for VOD propylaxis, and fibrinolytics for clotted lines allowed	Compression ultrasound ($n = 7$) and venography if required ($n = 4$)	Symptomatic CVC-related thrombosis adjudicated centrally by 2 blinded review individuals	DVT at other sites than CVC-associated veins, pulmonary embolisms	3 Major eps placebo, no major eps in the warfarin arm	5/125 (4.0%) placebo 6/130 (4.6%) warfarin $P = 0.68$
Karthaus et al. 2005	db, rd, 439 pts, multinational (12 countries), 48 centers	Dalteparin 5000 IU sc qd vs placebo, 2:1 randomization dalteparin : placebo	16 weeks, starting within 120–168 h after CVC-insertion	Heparin 500 IU portflushing allowed. Ass, coumadin not allowed	ipsi- + contralateral venography in 265 pts or compression ultrasound in the remaining pts for efficacy*	Symptomatic + asymptomatic CRC. Blinded central review for ipsi- and contralateral venograms, CT scans, compression ultrasonography	CRC/d; asymptomat. CRT, time to CRC or CVC removal; use fibrinolytic agents for CRT; CR infection; non CVC-related TEE	1 Major bleeding episode in both arms	3.7% dalteparin ($n = 11$) vs 3.4% placebo ($n = 5$) $P = 0.88$

*In Germany, venographies in patients <35 years were not permitted under the guidelines of the ethics committee.

external catheters. Eastridge and Lefor [31] prospectively evaluated 209 and 113 cancer patients who had received external catheters or subcutaneous ports, respectively. In the cohort of patients with external catheters a higher frequency of thrombosis (10% versus 6% in the cohort of patients with ports) was demonstrated. Data reported in patients who had implanted subcutaneous ports were confirmed by Lyon et al. [32]. These authors retrospectively evaluated 195 venous access devices implanted in cancer patients, and observed a catheter-related thrombosis rate and an infection rate of ~5%. In another small study, 100 cancer patients were randomized to receive an external catheter or subcutaneous port, and were monitored for catheter-related complications for 6 months [33]. Although the difference was not statistically significant, thrombotic complications (9% versus 2% of patients with ports) occurred in more often patients with external catheters. However, thus far, an older meta-analysis on limited patient numbers could not establish an effect of the type of catheter on CRC [34].

The low frequency of CRCs might also be discussed as a consequence of routine flushing of the catheter to maintain its patency. As pointed out in Table 7, port flushing was carried out in most clinical trials. In some trials, however, there was no statement on the practice of port flushing. Another point to be considered is the shorter hospitalization and the outpatient treatment that has become more common practice in the last 15 years. More frequent and longer admissions to the hospital seem to be associated with a higher frequency of thrombosis [35, 36].

In this trial dalteparin was well tolerated and there were no important differences in terms of overall safety when dalteparin was compared with placebo. Bleeding complications with a daily dose of 5000 IU administered for prophylaxis were observed less often when compared with LMWH or coumadin for treatment of thromboembolic events in cancer patients [29, 34, 37–39]. In particular, major bleeding occurred in only one dalteparin-treated (0.4%) and one placebo-treated patient, and dalteparin-related thrombocytopenia was also infrequent (0.7%). Regarding the adverse event analyses dalteparin appeared to be nearly as safe as placebo.

In conclusion, our results suggest that the actual risk for cancer patients carrying CVC to developing thrombotic events is overestimated and is not as high as suggested in earlier reports. In our study, dalteparin failed to reduce the low risk of thromboembolic complication in this study population but was well tolerated at a dose of 5000 IU daily.

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