ANTICANCER RESEARCH *25*: 3143-3148 (2005)

Prophylaxis of Central Venous Catheter-related Thrombosis with Minidose Warfarin: Analysis of Its Use in 427 Cancer Patients

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Abstract. *Background: In the past few years, several studies have been performed to evaluate thrombosis prophylaxis with warfarin in cancer patients with central venous catheters (CVC), but the analysis of these studies does not allow firm conclusions to be drawn. Patients and Methods: Four hundred and twenty-seven cancer patients were evaluated. Each received warfarin at a dose of 1 mg/daily as prophylaxis, starting the day after CVC positioning until its removal. Results: The catheters were monitored for a mean of 168 days (range 22-706). There were 9 thrombotic events (1.8%). Overall, International Normalised Ratio (INR) elevation occurred in 55 (12.8%) patients. Bleeding was observed in 15 (3.5%) patients, 10 of whom had elevated INR levels. Of these, all were treated with continuous-infusion 5-Fluorouracil (5-FU)-based regimens. Conclusion: Minidose warfarin can protect from clinical thrombosis, but can induce an alteration in INR values and/or haemorrhagic symptoms in patients being treated with 5-FU-based regimens.*

Indwelling central venous catheters (CVC) have become essential for the administration of many chemotherapeutic regimens. In a significant number of such patients, however, there are thrombotic complications (1), the causes of which are multifactorial. The malignant disease and/or its therapy are considered the most relevant factors (2, 3). The frequency of venous thromboembolism (VTE) in cancer patients ranges from 5%-10% compared to an incidence of 0.1% in the general population (4). The insertion of the CVC (5), CVC-induced abrasions of the endothelial walls (6), blood flow modifications (7) and the sclerosing nature of some chemotherapeutic agents (8) may all be factors in thrombosis development. In the past, several studies were performed to evaluate pharmacological prophylaxis with warfarin in cancer patients with CVCs, but the analysis of these studies has not allowed firm conclusions to be drawn. Some studies have shown that minidoses of warfarin (1 mg/day) reduced catheter-related thrombosis without usually inducing alterations in the prothrombin time (PT), activated partial thromboplastin time (aPTT) or causing bleeding (9, 10), whereas other studies have not supported the routine use of minidose warfarin in CVC prophylaxis (11, 12). Two retrospective studies have recently suggested a high incidence of elevation of the International Normalised Ratio (INR) in cancer patients treated with concomitant minidose warfarin and 5-Fluorouracil (5-FU)-containing regimens (13, 14). In the current study, the incidence of CVC-related clinical thrombosis and INR variation were retrospectively evaluated in a large cohort of haematological and non-haematological patients receiving prophylactic minidoses of warfarin.

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Key Words: Catheters, prophylaxis, warfarin, thrombosis, chemotherapy.

Patients and Methods

Patients. Four hundred and twenty-seven consecutive cancer patients (242 males and 185 females), treated with chemotherapy between July 2000 and May 2003, were evaluated. The patients' median age was 57 years (range 19-81). One hundred and fifty-six patients (36.5%) were affected by haematological malignancies and 271 (63.5%) had non-haematological malignancies. The catheters were monitored for a mean of 168 days (range 22-706). During warfarin prophylaxis, 142 (33%) patients received one chemotherapy regimen, 224 (52%) two chemotherapy regimens and 61 (15%) three or more regimens, respectively. Furthermore, 155 patients (36%) were given high-dose chemotherapy (HDT) followed by peripheral-blood stem-cell transplantation (PBSCT). In these 155 patients warfarin was interrupted during aplasia when platelet counts fell below 50,000/dl.

CVC-positioning and type. All patients had their CVC positioned by a radiologist in the outpatient angiographic room. All CVCs were

Table I. *Incidence of thrombotic complications in the 427 patients.*

	N.	%
Thrombotic events	9	1.8
Conventional chemotherapy	8	
High-dose therapy	1	
Median number of days between insertion and thrombosis (range)	152 (22-216)	
Type of CVC :		
Vygon	8/233	
Groshong	1/167	
Port-a-Cath	-/27	
Neoplasia		
HD	3	
NHL	2	
Sarcoma	2	
Leukemia	1	
Gastric cancer	1	

CVC: central venous catheter
HD: Hodgkin's disease
NHL: non-Hodgkin's lymphoma

Table II. *Analysis of risk-factors and thrombosis occurrence.*

Factor evaluated	*P* value
Sex	0.97
Age	0.27
Neoplasia	0.14
CT regimen	0.60
Number of previous courses of CT: 1 *vs* >1	0.69
Type of CVC	0.16

CT: chemotherapy
CVC: central venous catheter

placed on the right side with the area under local anaesthesia. The puncture of the subclavian vein was always performed under ultrasound guidance to avoid the risk of pneumothorax. The guidewire and catheter positions were evaluated by intraoperative fluoroscopy. Three types of CVC were used during the study period. Two-hundred and thirty-three patients (54.5%) had a Vygon catheter external device (NUTRICATH"S" 60 cm, NUTRICATH-VYGON, Vygon S.A., Encoven, France), 167 patients (39%) had a Groshong catheter external device (Bard Access System, Salt Lake City, UT, USA) and 27 (6.5%) patients had a Port-a-Cath (titanium port with attachable radio-opaque silicone 6.6Fr open-ended single lumen venous catheter; 76 cm length, 1.0 mm lumen; BardPort; Bard Access System), which is a completely internalized device

Treatment plan and evaluation. All patients received prophylactic oral warfarin at a fixed dose of 1 mg/day starting on the day of CVC insertion. The INR was measured every 3 weeks, with the prothrombin time being measured using "Hemoliance Recombiplastin" (Instrumentation Laboratory Inc.-Lexington, Lexington, USA); the normal value of INR was 0.90-1.18 with an INR of more than 1.5 regarded as being significantly elevated. Major bleeding was defined as soft tissue bleeding requiring blood transfusion, haematemesis, haemoptysis, melena, macrohaematuria, vaginal bleeding apart from that of normal menses, epistaxis for more than one hour with gross blood loss, or retinal haemorrhages with impairment of vision. Patients were clinically monitored for thrombotic complications from the day of line insertion through chemotherapy interruption, CVC dislocation, or patient's death. Routine radiological investigations to detect an asymptomatic CVC-related thrombosis were not performed. Patients were reviewed by the medical staff and investigated only if they complained of continuous pain from their central line or if there were clinical signs of venous thrombosis. Patients with clinically-suspected catheter-related or other venous thrombosis were investigated with doppler ultrasound and/or venography at the discretion of the clinician. Confirmed venous thrombosis was treated by removal of the CVC and full anticoagulation therapy. Statistical analysis was performed using Pearson's method.

Results

Overall, nine thrombotic events were observed, eight of which were directly related to the CVC. The eight events were subclavian vein thromboses, five of which were confined to the subclavian vein and three extended to the superior *vena cava*. The remaining event was a deep saphenous-vein thrombosis. The median time-interval between line insertion and thrombosis was 152 days (range 22-216 days) (Table I). Three patients were undergoing first-line treatment, three were receiving second-line treatment, and the others had received three or more regimens. Only one patient developed a thrombosis during high-dose therapy. All, but one, had Vygon catheters. The median age was 40 years. Five were males and four were females. Six patients were affected by haematological malignancies and three had solid tumours. A number of potential predictive factors including age, type of neoplasia, chemotherapy regimen, number of previous courses of chemotherapy at the time of presentation and type of catheter were analysed as possible predictors of thrombotic events without any significant correlation being found (Table II). INR elevation occurred in 55 (12.8%) patients. Of these, 17 patients had an INR of 2.0-2.9, 14 had an INR of 3.0-4.9 and 9 had an INR of at least 5.0. Major bleeding was observed in 15 (3.5%) patients, 10 of whom had elevated INR levels. Of these, all were non haematological patients receiving continuous-infusion 5-FU-based regimens. Considering only those patients treated with 5-FU-based

Table III. *Incidence of other complications*

	N.	%
Patients with INR elevated	55	12.8
Patients with bleeding	15	3
CVC removed before CT stopped or death	64	15
Reasons for removal		
CVC dislocation	44	
Infections	9	
Malfunctions	8	
Thrombosis	3	
Type of neoplasia		
MM	15	
NHL	14	
HD	13	
Colon cancer	11	
Sarcoma	11	
Type of CVC used		
Vygon	54	
Groshong	10	
Port-a-Cath	-	

INR : International Normalised Ratio
CVC: central venous catheter
CT: chemotherapy
MM: multiple myeloma
NHL : non-Hodgkin's lymphoma
HD: Hodgkin's disease

regimens, the incidence of INR elevation was 29%. All patients with INR abnormalities or bleeding had normal platelet counts and none had significantly abnormal hepatic parameters. Warfarin administration was discontinued at the first sign of INR elevation and, in all cases, this was resolved within 48 hours. Chemotherapy was then continued without warfarin prophylaxis. None of these patients showed any further INR elevation. Other complications during therapy are shown in Table III.

Conclusion

In cancer patients, the use of CVCs has markedly increased during the past few decades. The devices reduce the need to enter the venous system to draw blood samples and administer cytotoxic drugs, antibiotics, blood products, fluids and nutrition. Furthermore, central venous access is mandatory in the care of patients receiving intensive chemotherapy, and the harvest of peripheral stem cells is not possible without adequate access.

Although CVC devices are clearly advantageous, their placement and maintenance is not without potential complications, with one of the most common catheter-related risks being the development of a VTE. Previously published reports have indicated an incidence of symptomatic thrombosis of 5%-10% in patients with such implanted catheters (15). Furthermore, prospective studies in patients with cancer demonstrated radiographic evidence of deep venous thrombosis or occlusion in as many as two-thirds of patients with CVCs (16-18) and indicated that the first six weeks after CVC insertion is the time of greatest risk of thromboembolic complications. A dose of 1 mg of warfarin daily does not usually elevate the INR but, despite this apparent lack of a significant haemostatic effect, it is often used in clinical trials to prevent venous thrombosis in cancer patients (19, 20).

In 1990, Bern *et al.* (19) reported a significant reduction in catheter-related thrombosis in a randomised study of 82 cancer patients (37.5% *vs* 9.5%). Another study (13) evaluated the same dose of warfarin in 108 patients with haematological malignancies, in comparison with historical controls, and observed a significant reduction in the incidence of thrombosis (5%-13%). In contrast, a non-randomised trial involving 84 patients, also treated with minidose warfarin (11), showed no reduction in the clotting of catheters (13% *vs* 10%; p=n.s.), and another randomised trial in 88 patients found no benefit from the routine use of minidose warfarin for prophylaxis in patients with haematological malignancies (12). Finally, in a recent article (21) where the epidemiology, pathogenesis, diagnosis, prevention and treatment of VTE in cancer patients with long-term CVCs was reviewed, the authors concluded that the analysis of the studies in the world literature did not allow a firm conclusion on the clinical value of this approach to be drawn.

The reasons for this controversy are numerous. Most of the studies were open and of small sample size. Furthermore, the study end-point varied from venography-detected VTE in some studies to clinically overt thrombosis in others. No double-blind venography-based studies were performed. In addition, haemorrhagic complications were not fully described, despite the fact that bleeding is a major concern during administration of anticoagulants in cancer patients at risk of drug-related thrombocytopenia.

In our large cohort of patients, with a long follow-up period, minidose warfarin reduced clinical thrombosis associated with indwelling catheters in patients receiving chemotherapy both for haematological and non-haematological malignancies. In fact, only eight patients (1.8%) developed a clinical thrombosis in the subclavian vein in which the CVC was placed, and one occurred in the deep saphenous-vein. Of these nine thromboses, only two developed thrombosis within the first six weeks of insertion. Several possible predictive factors were analysed, but none

were found to be significant. It is of interest that only one case of thrombosis in the 155 patients undergoing high-dose therapy was observed despite the fact that, in the literature, a particularly high incidence of catheter thrombosis (up to 7%) has been associated with activation of coagulation markers in this context (22-27). This data suggests that the minidose of warfarin is also useful in this particular group of patients. Even though the occurrence of CVC-related thrombosis has been reported to be higher during the first weeks after insertion of CVC, this phenomenon was not observed in our cohort of patients, in whom thrombosis was detected up to seven months after CVC insertion. Consequently, a short course of prophylaxis around the time of CVC insertion does not seem appropriate and should not be recommended.

Another important consideration is the safety of minidose warfarin. This prophylaxis is generally considered safe, however, our group has recently reported the importance of monitoring the INR in patients receiving warfarin and 5-FU-containing regimens, mainly the FOLFOX regimen, because of a high incidence of INR elevation and bleeding (13, 14). The current study confirmed that patients undergoing continuous-infusion 5-FU-based chemotherapy, who were given concurrent minidose warfarin, had a high risk of both INR elevation and bleeding. In fact, considering only those patients treated with 5-FU-based regimens, the incidence of INR elevation and bleeding were 29% and 7%, respectively.

In conclusion, this study, in a large cohort of patients and over a long observation time, confirms the efficacy of minidose warfarin in reducing catheter-related thrombosis in haematological and non-haematological patients undergoing standard and/or high-dose chemotherapy and raises questions regarding the possible use of low-dose warfarin for primary thromboprophylaxis in all cancer patients. Furthermore, the study confirms a high incidence of INR elevation when minidose warfarin was given along with a 5-FU infusion. Clinicians should be aware of this interaction and should regularly monitor the prothrombin time of patients receiving warfarin and 5-FU.

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Received February 1, 2005
Accepted May 4, 2005