The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 9

Cohort study on the management of cancer-associated venous thromboembolism aimed at the safety of stopping anticoagulant therapy in patients cured of cancer

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ABSTRACT

Background

After diagnosis of cancer-associated venous thromboembolism (VTE), guidelines recommend considering the continuation of anticoagulant treatment until the patient is cured of cancer, although the safety of stopping anticoagulant treatment after the patient is cured has never been evaluated.

Methods

We conducted a cohort study in consecutive patients in whom cancer-associated VTE was diagnosed at the Leiden University Medical Center between January 2001 and January 2010 and monitored for the effect of cancer treatment, occurrence of recurrent VTE, major hemorrhage, and death.

Results

Of the 358 patients with cancer-associated VTE, anticoagulant treatment was continued until the death of 207 patients. In another 12 patients anticoagulant treatment was continued because of an alternative indication despite their being cured of cancer. Anticoagulant treatment was stopped in 50 patients for reasons other than major hemorrhage despite active cancer, in 21 patients after major hemorrhage, and in 68 patients after they had been cured of cancer. Among these 68 patients, 10 patients received a diagnosis of symptomatic recurrent VTE during a cumulative follow-up of 311 years, resulting in an incidence rate of 3.2 per 100 patient-years (95% CI, 1.5-5.9). Seven of these 10 patients with recurrent VTE experienced a cancer relapse during follow-up. For the 50 patients who stopped anticoagulant treatment despite active cancer the recurrent VTE incidence rate was 19 per 100 patient-years (11 events during 59 years of follow-up; 95% CI, 9.3-33).

Conclusions

Our data support the recommendation to stop anticoagulant treatment of cancer-associated VTE in patients cured of cancer. A cancer relapse seems to be a strong risk factor for recurrent symptomatic VTE.

INTRODUCTION

Venous thromboembolism (VTE) is a well-recognized complication in the course of cancer and causes significant morbidity and mortality. Arterial and venous thromboembolism has been reported to be the second leading cause of death among patients with cancer, after cancer itself [1]. Also, all-cause mortality is higher in patients with cancer-associated VTE compared with matched patients with cancer but without concomitant VTE [2]. Established risk factors for cancer-associated VTE include metastatic disease, the presence of central venous catheters, chemotherapy, recent surgery, and immobilization [3-4].

Treatment of cancer-associated VTE is challenging because of the high risk of both recurrent VTE and major hemorrhage under anticoagulant treatment, with hazard ratios of 3.2 (95% confidence interval [CI], 1.9-5.4) and 2.2 (95% CI, 1.2-4.1), respectively, compared with patients with VTE but without cancer. The 12-month cumulative risk of recurrent VTE and major hemorrhage in patients with cancer while receiving anticoagulant treatment has been reported to be as high as 21% and 12%, respectively, compared with 6.8% and 4.9% in patients without cancer [5]. Both the type of anticoagulant treatment and the optimal duration of treatment have been debated [6-9]. In the absence of evidence from clinical trials, treatment of cancer-associated VTE beyond the initial 6 months after diagnosis remains controversial. Since the risk of recurrent VTE after the initial 6 months is believed to remain high, some authors have considered continuing anticoagulant treatment as long as the cancer is active [7-8,10-11]. The American Society of Clinical Oncology guideline recommends considering continuation of anticoagulant treatment only for selected patients with active cancer, such as patients with metastatic disease or those receiving chemotherapy [11]. On the other hand, some patients with cancer-associated VTE successfully complete a curative anticancer treatment, for instance, radical surgery or adjuvant chemotherapy, and in these patients the VTE recurrence risk is assumed to be low since the provoking factor is no longer present. Consequently, in these patients who are cured of cancer anticoagulant treatment could possibly be stopped, although the safety of treatment withdrawal has never been investigated [7-8,10]. Therefore, we evaluated the treatment of cancer-associated VTE in daily clinical practice, with the aim of determining the safety of stopping anticoagulant therapy in patients cured of cancer.

MATERIALS AND METHODS

Patients

This was an observational chart review study including all consecutive patients in whom cancer-associated VTE was diagnosed in the period from January 2001 to January 2010 at the Leiden University Medical Center (Leiden, the Netherlands). VTE was defined as a diagnosis of either pulmonary embolism (PE), lower extremity deep vein thrombosis (DVT), or upper extremity DVT. PE had to be confirmed by contrast-enhanced CT scan or by ventilation-perfusion (V/Q) lung scan, and DVT had to be confirmed by (compression) ultrasonography or CT venography in accordance with current guidelines [7,12]. Patients with symptomatic VTE as well as those with incidentally diagnosed VTE were included in this study. Active cancer was defined as cancer diagnosed within 6 months of the diagnosis of VTE (excluding basal cell or squamous cell carcinoma of the skin), recently recurrent or progressive cancer, or any cancer that required anticancer treatment within the 6 months preceding the diagnosis of VTE. Patients with solid malignancies as well as those with hematologic malignancies were eligible.

Patients with cancer-associated VTE were treated according to local clinical practice. Before 2007, standard treatment of cancer-associated VTE was initially low-molecular-weight heparin (LMWH) or unfractionated heparin followed by long-term vitamin K antagonists (VKA). From 2007, standard treatment consisted of weight-adjusted therapeutic nadroparin (171 International Units of anti-factor Xa/kg once daily). The initial duration of treatment of cancer-associated VTE was 3 to 6 months. Thereafter an indefinite duration of treatment was considered for all patients with active cancer, although the guideline allowed physicians to consider a limited duration of treatment after weighing the risk of recurrent VTE and the risk of major hemorrhage. For patients with an upper extremity DVT associated with a central venous catheter that was removed, the standard duration of treatment was 4 weeks after removal of the central venous catheter. Incidentally diagnosed and symptomatic VTE were treated in the same way [7-8,10]. The institutional review board of the Leiden University Medical Center approved the study and waived the need for informed consent.

Study Aims, End Points, and Follow-up Procedures

The primary aim of this study was to determine the incidence rates of recurrent VTE and major hemorrhage after stopping anticoagulant treatment in patients who were considered to be cured of cancer. The secondary aims were (1) to evaluate the clinical course if a cancer relapse or new cancer was diagnosed, (2) to determine the incidence rates of recurrent VTE and major hemorrhage after anticoagulant treatment was stopped for reasons other than major hemorrhage in patients with active cancer, and

(3) to determine the incidence rates of recurrent VTE and major hemorrhage in patients while receiving anticoagulant treatment.

Recurrent PE was defined as a new intraluminal filling defect on pulmonary angiography or computed tomographic pulmonary angiography, a new high-probability perfusion defect on V/Q scan or any new defects after earlier normalization of the scan, or confirmation of a new PE at autopsy. V/Q scans were evaluated according to PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) criteria. Recurrent lower extremity DVT was defined as new noncompressibility by ultrasonography of the common femoral and/or popliteal vein in the transverse plane or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm). Recurrent upper extremity DVT was defined as evidence of VTE in the subclavian, axillary, and/or brachial vein on ultrasonography or CT venography [12]. Incidentally diagnosed VTEs detected on imaging for oncologic staging were not counted toward the end points in this study, since it is highly complicated to decide whether signs of VTE on a nondedicated imaging test after the initial VTE represent recurrent or residual VTE.

Secondary end points included fatal PE, major hemorrhage, fatal hemorrhage, a cancer relapse, a new diagnosis of cancer, and death. Major hemorrhage was defined in accordance with the International Society on Thrombosis and Haemostasis criteria [13]. The cause of death was verified by reviewing medical records and, if available, the pathology.

All patients were monitored regularly in the context of standard clinical care by their oncologist for new signs or symptoms of a malignancy according to relevant oncology guidelines, as well as the occurrence of symptomatic recurrent VTE. Patients were monitored until their last visit to our hospital, until death, or until September 2014. Medical records were reviewed by two reviewers for the occurrence of end points of the study (T. v. d. H. and P. v. d. H.).

Patients were considered to be cured of cancer or "in complete remission" when the following criteria were fulfilled: (1) there were no signs and symptoms suggestive of residual or recurrent disease; (2) anticancer treatment with a curative intent had been completed, including adjuvant hormonal therapy and chemotherapy; (3) a reasonable chance of cure existed, taking into account the cancer type and stage (ie, nonmetastatic disease or an objectively determined response to treatment). The final decision as to whether a patient was considered to be cured was made by the treating oncologist. A new diagnosis or a recurrence of cancer had to be confirmed by tissue sampling.

Analyses and Statistics

To provide an overview of the total cohort, 6- and 12-month cumulative incidence rates of recurrent VTE, major hemorrhage while receiving anticoagulant treatment, and death

were calculated according to the Kaplan-Meier method, starting at the time of diagnosis of cancer-associated VTE.

For analysis of the primary and secondary end points, follow-up started at the time anticoagulant treatment was stopped and censored at the time of a recurrent VTE, major hemorrhage, death, or last follow-up, whichever came first. Incidence rates were calculated according to the Kaplan-Meier method with 95% CI. No direct comparisons between patient groups were performed.

All analyses were repeated after excluding patients with an incidentally diagnosed VTE. Data were analyzed with SPSS version 20 (SPSS Inc).

RESULTS

Three hundred and fifty-eight patients received a diagnosis of cancer-associated VTE (**Table 1**). The mean age was 59 years (SD, 15), 189 patients (53%) were male, and 282 patients (79%) had metastatic cancer. Two hundred and thirty-one patients (65%) had PE (with or without DVT), 96 patients (27%) had an isolated DVT of the lower extremities, and 31 patients (8.7%) had an isolated DVT of the upper extremities. VTE was incidentally diagnosed in 61 patients (17%), of whom 55 patients had PE, five patients had lower extremity DVT, and one patient had upper extremity DVT. Only in 17 of the 231 patients (7.4%) with PE was the diagnosis based on a V/Q scan; of these, two patients also received a diagnosis of DVT. In the remaining 214 patients with PE the diagnosis was based on CT scan. Of the 358 patients, 142 patients (40%) were treated with long-term LMWH, 205 patients (47%) with VKA, nine patients (2.5%) were treated with intravenous unfractionated heparin, one patient (0.3%) was in a terminal phase of cancer and anticoagulant treatment was withheld, and one patient (0.3%) was treated with an inferior vena cava filter only because of concurrent major hemorrhage. For the total cohort, the 6- and 12-month cumulative mortality risks were 45% (SE, 0.026) and 57% (SE, 0.026), respectively. Of the 204 patients who died within the first 12 months of follow-up, the cause of death was directly related to the cancer in 167 patients (82%). Six patients (2.9%) had a fatal hemorrhage; seven patients (3.4%) had a (high suspicion of) fatal PE; 20 patients (9.8%) died of another, directly related cause; and in four patients (2.0%) the cause of death was unclear. Thirty-three recurrent VTE events occurred among patients while receiving anticoagulant treatment during a cumulative follow-up of 282 years, for an incidence rate of 12 per 100 patient-years (PY) (95% CI, 8.1-16). Major hemorrhage occurred in 53 patients while receiving anticoagulant treatment during a cumulative follow-up of 240 years, for an incidence rate of 22 per 100 PY (95% CI, 17-29). Outcomes while receiving anticoagulant treatment were comparable between patients with inci-

Table 1. Patient characteristics.

Characteristic	Total cohort n=358	AC stopped after cure from cancer n=68	AC stopped for reasons other than major haemorrhage despite active cancer n=50
Mean age (SD)	59 (15)	53 (17)	56 (15)
Male sex, n (%)	189 (53)	35 (51)	27 (54)
Previous VTE, n (%)	30 (8.4)	3 (4)	6 (12)
Metastatic cancer, n (%)	282 (79)	38 (56)	43 (86)
Surgery < 4 weeks, n (%)	64 (18)	25 (37)	5 (10)
Immobilization <4 weeks, n (%)	157 (44)	44 (65)	20 (40)
Incidentally diagnosed, n (%)	61 (17)	14 (21)	6 (12)
Cancer type, n (%)			
Lung	54 (15)	2 (3)	4 (8)
Colorectal	24 (7)	3 (4)	3 (6)
Other gastrointestinal	42 (12)	10 (15)	2 (4)
Breast	28 (8)	0 (0)	7 (14)
Testicular	15 (4)	11 (16)	2 (4)
Gynaecological	22 (6)	6 (9)	5 (10)
Central nervous system	10 (3)	0 (0)	1 (2)
Other solid	98 (27)	17 (25)	9 (18)
Multiple Myeloma	10 (3)	2 (3)	6 (12)
Non-Hodgkin lymphoma	22 (6)	7 (10)	5 (10)
Other haematological	33 (9)	10 (15)	6 (12)
Type of VTE, n (%)			
PE (±DVT)	231 (65)	48 (71)	31 (62)
Lower extremity DVT	96 (27)	15 (22)	14 (28)
Upper extremity DVT	31 (9)	5 (7)	5 (10)
Treatment, n (%)			
LMWH	142 (40)	30 (44)	11 (22)
VKA	205 (57)	38 (56)	39 (78)
Other/none	11 (3)	0 (0)	0 (0)

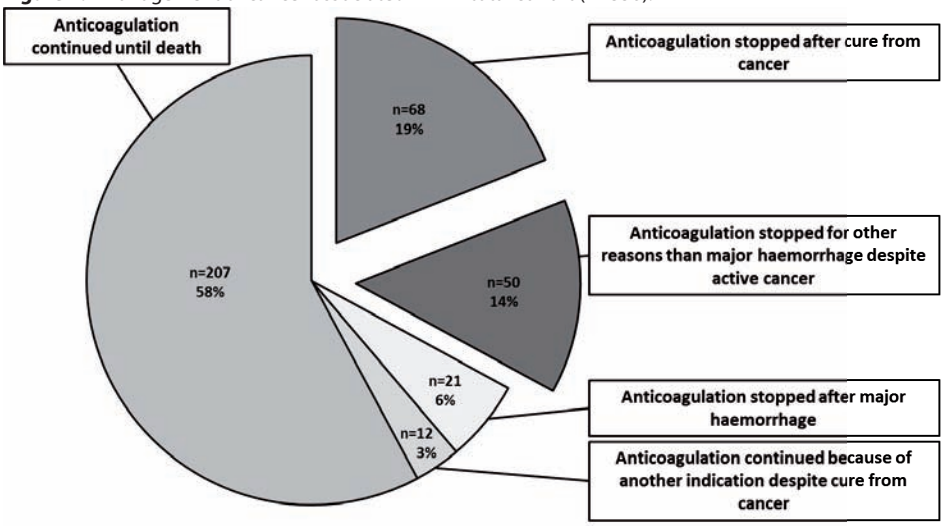
Note: AC: anticoagulation; SD: standard deviation; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; LMWH: low-molecular-weight-heparin; VKA: vitamin K antagonists.

dental VTE and those with symptomatic VTE, and in the period 2001-2005 compared with 2006-2010 (data not shown).

Patients Cured of Cancer

Of the 358 patients, 80 patients (22%) were cured of cancer during follow-up, of whom 12 patients had another indication for continuing anticoagulant treatment: eight patients received a diagnosis of atrial fibrillation, two had a persistent vena cava inferior filter, one patient had a history of recurrent VTE, and one patient was immobilized (**Figure 1**). In the remaining 68 patients, whose baseline characteristics are shown in **Table 1**, anticoagulant treatment was stopped after a median duration of 6.0 months (interquartile range, 4.7-6.7 months).

Figure 1. Management of cancer-associated VTE in total cohort (n=358).



After anticoagulant treatment had been stopped, 10 patients had a symptomatic recurrent VTE during a cumulative follow-up of 311 years, for an incidence rate of 3.2 per 100 PY (95% CI, 1.5-5.9) (**Figure 2, Table 2**). Three of these patients had PE, five patients had a lower extremity DVT, and two patients had an upper extremity DVT. No incidental VTEs were diagnosed among these patients. In 15 of the 68 patients (22%) a cancer relapse was diagnosed, and three patients (4.4%) received a diagnosis of a new primary malignant tumor. Of the 10 recurrent VTE events, seven events occurred in patients who also experienced a cancer relapse: five occurred in patients who shortly before or at the same time received a diagnosis of a cancer relapse, two patients experienced a cancer relapse 9 and 14 months after the recurrent VTE event, and three patients remained free of a cancer relapse. Seven of the 15 patients (47%) with a cancer relapse also experienced a recurrent VTE. A major hemorrhage occurred in four of the 68 patients after anticoagulant treatment was stopped during a cumulative follow-up of 303 years, resulting

in an incidence rate of 1.3 per 100 PY (95% CI, 0.4-3.4). None of the major hemorrhages occurred in patients in whom a cancer relapse or new cancer was diagnosed.

Patients Not Cured of Cancer in Whom Anticoagulant Treatment Was Stopped

In 50 of the 278 patients with active cancer, anticoagulant treatment was stopped for reasons other than the occurrence of a major hemorrhage after a median duration of 5.8 months (interquartile range, 3.9-6.5 months). In nine of these 50 patients a reason for stopping anticoagulant treatment was documented, that is, a supposed high risk of major hemorrhage or frequently planned invasive procedures. In the remaining 41 patients a limited duration of treatment was considered to be sufficient, although it cannot be completely excluded that this decision was influenced by the presence of any relative contraindication, for instance, an estimated higher-than-standard risk of major hemorrhage. After anticoagulant treatment was stopped, a nonfatal recurrent VTE developed in 11 patients during a cumulative follow-up of 59 years, resulting in an incidence rate of 19 per 100 PY (95% CI, 9.3-33) (**Figure 2, Table 2**). A major hemorrhage occurred in three patients after anticoagulant treatment was stopped during a cumulative follow-up of 59 years, for an incidence rate of 5.1 per 100 PY (95% CI, 1.1-15).

Table 2. Risk of recurrent VTE and major haemorrhage.

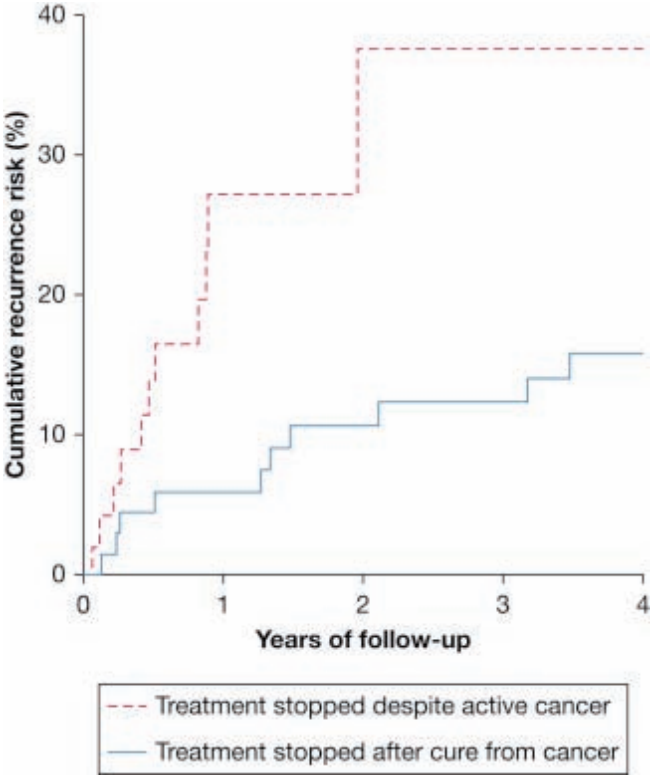
	Events / cumulative follow-up Incidence rate (95% CI)	
Category	**Recurrent VTE**	**Major haemorrhage**
While on anticoagulant treatment for total cohort	33 / 282 years 12 / 100 PY (8.1-16)	53 / 240 years 22 / 100 PY (17-29)
Anticoagulant treatment stopped after cure from cancer	10 / 311 years 3.2 / 100 PY (1.5-5.9)	4 / 303 years 1.3 / 100 PY (0.4-3.4)
Anticoagulant treatment stopped for reasons other than major haemorrhage despite active cancer	11 / 59 years 19 / 100 PY (9.3-33)	3 / 59 years 5.1 / 100 PY (1.1-15)

Note: VTE: venous thromboembolism; CI: confidence interval; PY: patient years.

DISCUSSION

The key finding of our study is the 3.2-per-100 PY (95% CI, 1.5-5.9) incidence rate of recurrent VTE in patients whose anticoagulant treatment was stopped after they were cured of cancer. This rate is fully comparable to the VTE recurrence rate of 3.3 per 100 PY (95% CI, 2.8-3.9) after stopping anticoagulant treatment in patients with a first VTE related to a transient provoking factor, in whom a 3- to 6-month duration of anticoagulant

Figure 2. Cumulative incidence rate of recurrent VTE and major haemorrhage in patients who stopped anticoagulation after cure from cancer (straight line) and after stopping anticoagulation for other reasons than major haemorrhage despite active cancer (dotted line).



treatment is generally accepted [7-8,14]. Also, the incidence rate of recurrent VTE after stopping anticoagulant treatment can be weighed relative to the risk of major hemorrhage associated with long-term anticoagulant treatment, which has been estimated to be 2.74 per 100 PY (95% CI, 2.71-2.77) [15]. Since the case fatality rate for a major hemorrhage has been reported to be higher than that for a recurrent VTE, one ought to consider the clinical impact of major hemorrhage to be at least comparable to that of recurrent VTE. On the basis of both comparisons, we conclude that stopping anticoagulant treatment of cancer-associated VTE in patients who are cured of cancer is justified. Although this is in accordance with current guidelines, this is to our knowledge the first study supporting this recommendation [7-8].

A second important observation from our study is the association between cancer relapse and the risk of recurrent VTE: 47% of the patients with a prior cancer-associated VTE event who experienced a cancer relapse were diagnosed with recurrent VTE. From another point of view, 70% of recurrent VTE events occurred among the patients with a cancer relapse. Given these results, although based on small numbers of patients,

the question arises whether patients with cancer and previous cancer-associated VTE are candidates for ambulatory pharmacologic VTE prophylaxis. Until now, it has been proven difficult to identify patients with cancer who would benefit from thromboprophylaxis [16-17]. The Khorana prediction score has been developed for this purpose, and in a validation cohort with an overall PE incidence of 2.1% during 2.5 months of follow-up this score was successfully used to differentiate between patients with low, intermediate, and high risk of VTE (0.3%, 2.0%, and 6.7%, respectively) [18]. Whether the Khorana score is sufficient to identify patients at such a high risk that VTE prophylaxis is justified remains to be determined in a management study. Interestingly, this score does not award points for a history of VTE since this information was unavailable in the derivation cohort. Therefore, it seems relevant to investigate whether a history of (cancer-associated) VTE should be incorporated in prediction scores in future outcome studies.

Our study provides further insight in the long-term treatment of cancer-associated VTE in patients with persistently active cancer. The 19 per 100 PY incidence rate of recurrent VTE in patients in whom anticoagulant treatment was stopped for reasons other than major hemorrhage confirms the persistently high risk of recurrent VTE beyond the initial 6-month period. It should be emphasized that in some of these patients anticoagulant treatment was stopped, based on an assessment of the risk-to-benefit ratio of continued anticoagulant treatment. This finding should, therefore, be interpreted cautiously.

The observational study design in a single academic hospital is the most important limitation of our study. As a result, the number of included patients cured of cancer was limited, our population may differ somewhat from those in other hospitals, and outcomes may not have been noted in the medical records and therefore missed in this study. Also, recommendations regarding the treatment of cancer-associated VTE changed during the study period, with LMWH replacing VKA as the treatment of choice being the most notable difference. However, the primary outcome of this study was to determine the risk of recurrent VTE after stopping anticoagulant treatment, which is unlikely be influenced by the type of initial treatment. The major strength of this study is the description of all patients with cancer-associated VTE, which enables the assessment of the external validity. The overall survival as well as the outcomes of patients while receiving anticoagulant treatment are in line with results from other studies on cancer-associated VTE [5,19-20].

In conclusion, the VTE recurrence rate after stopping anticoagulant treatment of a cancer-provoked VTE in patients cured of cancer is low, which justifies stopping anticoagulant treatment in these patients. A cancer relapse in the further clinical course is a strong risk factor for recurrent VTE. Whether patients with cancer and a history of (cancer-associated) VTE warrant secondary pharmacologic VTE prophylaxis should be the focus of future studies.

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