CHEST

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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BACKGROUND: After diagnosis of cancer-associated 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. CHEST 2016; 149(5):1245-1251

KEY WORDS: cancer; DVT; pulmonary embolism

ABBREVIATIONS: LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PY = patient-year; V/Q = ventilation-perfusion; VKA = vitamin K antagonists

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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% 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). VTE was defined as a diagnosis of either pulmonary embolism (PE), lower extremity 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 (VKAs). 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