Cancer, thrombosis and low-molecular-weight heparins
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CHAPTER 1

INTRODUCTION

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BACKGROUND

Since Trousseau’s time, the clinical association between cancer and venous thromboembolism (VTE) has been observed and documented (1). The relationship between cancer and VTE insist on a two way clinical correlation. In fact it has been clearly established that cancer patients exhibit a higher risk of developing a thrombotic event when compared to non-cancer patients, especially in the presence of the well-known risk factors for thrombosis, such as prolonged immobilization, surgery and chemo-radio-hormonal therapy. It has also been clearly noticed that a first episode of idiopathic VTE may represent the first manifestation of a yet undisclosed cancer, offering chances for an earlier diagnosis of the pathology (2,3,4).

A substantial number of cancer patients receive anticoagulants either for prophylaxis, due to the high risk of developing thrombosis, or for treatment of an already established thrombotic event. The initial treatment of VTE in cancer patients should not differ from that of non cancer patients. In fact they will receive UFH or LMWH at therapeutic dosages. They begin also with warfarin. Once the INR has reached the therapeutic target, heparin or LMWH can be stopped and warfarin is continued for the remainder of the treatment period (4).

Cancer patients are at high risk of recurrent VTE when anticoagulation is stopped: studies conducted during the past decade, assessing the clinical course of patients with thrombosis, have documented that the risk of recurrence increases progressively in the course of time, being as high as 30% after 10 years from the thrombotic event. If risk factors for recurrence are considered, malignancy is the most common, being more frequent than thrombophilia. For these reasons, in patients with cancer and thrombosis, anticoagulation is recommended for as long as cancer is active (2,5).

Moreover cancer patients are at higher risk of both recurrence and major bleeding complications during anticoagulation, even if they are within the therapeutic range. Several published clinical trial have examined the administration of long-term LMWH as an alternative to warfarin therapy in cancer patients with VTE. There is strong evidence that LMWH is more efficacious than warfarin for preventing symptomatic recurrent VTE in cancer patients (4,6).

A complex relation exists between the coagulation system and cancer. Hemostasis and malignancy share linking mechanisms so that it has been noticed that the inhibition of hemostasis activation may impact on outcomes from malignancy. In particular LMWH may have potential antitumor effects. Further evaluations is warranted to assess if anticoagulation has the potential to prolong survival in cancer patients (7,8).

The incidence of newly diagnosed cancer during the follow-up of patients with VTE is higher than in the general population. VTE, especially in its idiopathic presentation, may represent the first manifestation of a yet undisclosed cancer, offering a possible chance for early diagnosis and treatment. Newly diagnosed malignancies are not confined to certain subtypes, but involve virtually all body systems. Some of these malignancies can be identified by routine assessment at the time of the diagnosis of the thrombotic event. Moreover, in patients with idiopathic VTE, who are apparently cancer free at baseline, there remains an approximate 7-10% incidence of clinically overt malignant disease during the follow-up period after the thrombotic event (1,2,9).
OUTLINE OF THE THESIS

Part A “Venous thromboembolism in cancer patients”

In chapter 2 we have analysed the two way clinical correlation between cancer and venous thromboembolism presenting data from three review articles which have examined epidemiology, risk factors, prophylaxis and treatment of VTE in cancer patients (1,2,3).

The risk of recurrent VTE and bleeding complications during anticoagulant treatment in cancer patients is presented in chapter 3. In this prospective follow-up study we sought to determine whether in patients with established thrombosis those with cancer are at higher risk for recurrent venous thromboembolism or bleeding complications during anticoagulant treatment than those without cancer. It has been demonstrated that cancer patients with venous thrombosis are more likely to develop recurrent thromboembolic complications and major bleeding during anticoagulant treatment than those without malignancy. These risks correlate with the extent of cancer (5).

Chapter 4 deals with the predictors of recurrent VTE or major bleedings in cancer patients with VTE, examining some variables available at entry among patients from the RIETE International Registry. We tried to identify which cancer patients are at a higher risk for recurrent pulmonary embolism (PE), deep vein thrombosis (DVT) or major bleeding. On multivariate analysis, patients aged <65 years, or with <3 months from cancer diagnosis to VTE had an increased incidence of recurrent PE or DVT. Finally, patients with immobility, metastases, recent bleeding, or with creatinine clearance <30 ml/min, had an increased incidence of major bleeding (10).

In chapter 5 current evidence on the most appropriate initial and long-term treatment of cancer patients with VTE as well as VTE prophylaxis was addressed. The management of recurrent VTE despite anticoagulation, the management of incidentally detected isolated pulmonary embolism (PE), the potential role of the novel direct oral anticoagulants and the impact of low-molecular-weight heparin (LMWH) on cancer evolution were considered (3,6).

Part B “Venous thromboembolism and the risk of cancer “

In chapter 6 we focus on the hot topic of the risk of hidden cancer in patients with idiopathic VTE, discussing on the need to screen patients with idiopathic VTE and no clinical evidence of cancer at the time of the index thrombotic event for occult malignancies. In fact, the high incidence of newly discovered cancers does not automatically imply that screening is indicated in these patients, since it is unknown whether a substantial proportion of cancers can be diagnosed, whether the diagnosed cancers are treatable and what the impact on cancer-related mortality is. Proper clinical trials are being conducted to find answer to these questions (9).
In **Chapter 7**, evidence has been provided in favour of extensive screening procedures for cancer identification to be performed among patients with a first episode of idiopathic VTE in whom a routine initial screening for cancer identification is negative. Arguments originate from available literature on this topic (10).

In **Chapter 8**, we presented the SOMIT study, a prospective evaluation in which apparently cancer-free patients with acute idiopathic venous thromboembolism were randomized to either the strategy of extensive screening for occult cancer or to no further testing. Patients had a 2-year follow-up period. Although early detection of occult cancers may be associated with improved treatment possibilities, it is uncertain whether this improves the prognosis (12).

In **Chapter 9**, a decision analysis from the data of the SOMIT-trial is presented. The screening tests were divided in several possible strategies. The number of detected cancers and the number of patients who underwent further investigations eventually ending in a benign condition, were calculated for each strategy and the total costs were determined. Based on tumor type, stage, age and gender of the individual cancer patient, the difference in life-years gained (LYG) was calculated between the two study groups. It has been found that the screening for cancer including abdomino/pelvic CT with or without mammography and/or sputum cytology appears potentially cost effective in patients with idiopathic VTE (13).

**Chapter 10** presents the D’Acquapendente Study, a randomized open label trial among patients with a first episode of idiopathic VTE and a normal baseline routine screening, which compared an extensive compound strategy based of CT scan of thorax, abdomen and pelvis plus haemoccult to a common clinical practice strategy based on the attending physician preference (but excluding CT as a first line test) for the identification of hidden cancer (14).

**Chapter 11** and **Chapter 12** deals with the long-term risk of cancer in patients with VTE. In patients with VTE, 15-20% will have overt cancer when VTE is diagnosed but little is known about such patients’ long-term risk, time course and predictors of new cancer. In patients with a first VTE and without clinically evident cancer, the risk for new cancer is about 1-2% per year, appears to be uniform over time, and is higher in patients with unprovoked VTE and those with advanced age. Moreover the risk of cancer in patients with VTE does not exceed that expected in the general population after the first 6 months (15,16).

**Part C. Effect of low-molecular-weight heparins on survival in cancer patients**

The association between cancer and activation of blood coagulation has been described since Trousseau’s time (1). The hypercoagulable state often encountered in cancer patients not only acts as an important risk factor for thrombosis, but also may play a role in tumour progression and metastatization. An anti-neoplastic effect of anticoagulants in this setting has often been hypothesized. The results of recently conducted clinical trials suggest that cancer patients could benefit from the administration of low molecular weight heparins, particularly those with
nonadvanced disease. Additional clinical trials are needed to provide further insight into this challenging setting. Studies in cancer patients with venous thromboembolism suggested that low molecular weight heparin may prolong survival. Chapter 13 is an overview of the current knowledge in this field (17) and chapter 14 presents the results of a trial among patients with metastasized or locally advanced solid tumours, who were randomly assigned to receive a 6-week course of subcutaneous nadroparin or placebo. The primary efficacy analysis was based on time from random assignment to death. The primary safety outcome was major bleeding (18).
References


