Venous thrombosis in cancer patients: Prediction, diagnosis and management
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1.

Introduction

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In 2008, a male patient of 45 years of age with pancreatic cancer came for his first cycle of chemotherapy at the outpatient clinic of the Academic Medical Center in Amsterdam. While talking with the nurses, he mentioned that he thought God had given him his first chemotherapy the night before, because as he woke up, he noticed multiple red stripes on his legs and arms. And indeed, physical examination showed palpable cords in the course of several superficial veins.

This story illustrates one of the rare presentations of the prothrombotic state in cancer patients, namely migrating thrombophlebitis (1). This condition is also called the ‘Trousseau syndrome’, named after the person who was actually the second to describe the relationship between cancer and venous thrombosis (2). At present, almost 200 years after the first description by Bouillaud in 1823, there are medical conferences specific on this topic, of which the increasing popularity indicates the clinical relevance of this condition, as well as the multiple gaps in our knowledge on venous thrombosis in cancer.

Almost 10% of all cancer patients will develop venous thromboembolism (VTE), i.e. pulmonary embolism or deep vein thrombosis, at one point during their disease, leading to significant morbidity and mortality (3-5). The occurrence of VTE in a cancer patient can almost never be traced back to one specific causal factor, but is rather multi-factorial. The cancer in itself is important, as the risk for VTE differs among the different cancer types and increases with increasing stage. Patient factors which play a role are immobility, older age and thrombophilic abnormalities. And lastly, the treatment for cancer is important, since chemotherapy (including a heterogeneous mix of medicines), but also radiotherapy, surgery and hormonal therapy are clear risk factors (6-9).

In recent years, much energy has been spent on the prediction of VTE in cancer patients. Knowing which cancer patients have an exceptionally high risk would enable targeted thromboprophylaxis of only those patients. One approach to the prediction of VTE in cancer is the use of clinical prediction models, the most well known example is the model developed by Khorana and colleagues (10). The clinical usefulness of models, however, can be questioned in view of the many factors influencing the risk, of which some change over time, e.g. as new chemotherapeutic (combinations) are being developed. Moreover, the performance critically depends on the population from which the prediction factors are derived. Therefore, a more promising approach is the use of biomarkers which are ideally pathophysiologically linked to the occurrence of the event of interest.

Microparticles are attractive candidate predictive biomarkers for VTE in cancer. Microparticles are cell-derived vesicles, sized 100 nm to 1 um, which can be shed from virtually every cell upon stimulation or activation and which circulate in body fluids. There is good evidence that microparticles are no innocent bystanders in the development of VTE in cancer. Already in 1981, Dvorak and colleagues demonstrated that several cancer cell lines release procoagulant plasma membrane vesicles (i.e. microparticles), which ranged in size between 15 to 800 nm (11). These microparticles are procoagulant as they provide phospholipids and thereby a surface for assembly of tenase and prothrombinase...
complexes, and, second, they can expose tissue factor (TF), the main initiator of coagulation (12;13). Subsequent human studies showed that the procoagulant state in cancer is mainly characterised by activation of the extrinsic clotting system, with increased factor VII and TF activity (14). In the plasma of cancer patients increased levels of microparticles exposing TF, have been found, as compared to healthy subjects (15). Moreover, cancer patients with VTE had higher numbers and coagulant activity of TF-exposing microparticles when compared to cancer patients without VTE (16;17). Therefore, TF-exposing microparticles have gained interest as potential predictive biomarkers for the development of VTE in cancer patients.

The diagnosis of lower limb DVT or pulmonary embolism has been studied extensively, and is in general not different in cancer patients when compared to non-cancer patients. Upper extremity DVT (UEDVT) is a relatively rare condition, only 5-10% of all deep vein thromboses concerns UEDVT. One of the main causes is malignancy or the use of venous catheters (18). Whereas a diagnostic algorithm comprising of a clinical decision score, D-dimer testing and ultrasonography has been widely established for the diagnosis of DVT of the leg and pulmonary embolism, the diagnostic work-up of patients with clinically suspected UEDVT is less well studied. Although contrast venography is the gold standard, it is largely being replaced by ultrasonography, because of its invasiveness. The safety and efficacy of ultrasonography, however, has only been studied in relatively small series (19). Recently a clinical score has been developed specifically for UEDVT by Constans and colleagues (20). An algorithm combining the Constans’ score, D-dimer testing and repeated ultrasonography, would be clinically attractive, but has not been tested so far.

The management of VTE in cancer patients is different compared to non-cancer patients. Cancer patients have an increased risk for both recurrent VTE and bleeding during anticoagulant treatment. The Clot study in 2003 demonstrated that long-term treatment with low molecular-weight heparin (LMWH) gives a 50% reduction in the risk of recurrent VTE when compared to the standard treatment with vitamin K antagonists (VKA) (21). The superiority of LMWH is confirmed by smaller studies and two meta-analyses (22-24). Major guidelines therefore recommend or suggest the use of LMWH for the long-term treatment (25;26). Still, questions remain on this topic, such as the dose and duration of the LMWH treatment, and the observance of the guidelines.

| OUTLINE OF THE THESIS |

In the first part of this thesis, we studied the roles of microparticles in cancer progression and VTE, and potential applications of subtypes of microparticles as predictive biomarkers. In chapter 2, a narrative review, we have provided an overview of the many different roles that microvesicles (i.e. microparticles and exosomes) play in cancer progression and the development of VTE in cancer. Mainly in vitro studies have provided insights in the patho-physiological mechanisms underlying the cancer progression stimulating effects of microparticles, e.g. by stimulating angiogenesis, or by inhibiting the immune response
directed to the cancer cells. In chapter 3 we were interested in the in vivo characteristics of microparticles in cancer patients. CD24 is a ligand of P-selectin, and when exposed on cancer cells, is correlated with a poorer prognosis (27). Therefore, we hypothesized that CD24-exposing microparticles would circulate, and they would also be associated with a worse prognosis. Chapter 4 describes a pilot study in which we looked for differences in general coagulation activation markers and microparticle dependent coagulation activation between 22 healthy subjects and 43 cancer patients. In chapter 5 we report an in-house developed plasma recalcification test, the fibrin generation test. The test measures the coagulant potential in platelet poor plasma, which is the product of the plasma coagulation factors and circulating microparticles. By adding an inhibitory antibody to activated factor VII (which complexes with TF), the contribution of TF-exposing MP to the clotting time can be quantified. In chapter 6 we investigated the numbers and coagulant activity of the TF-exposing microparticles circulating in a cohort of over 200 cancer patients. In those patients with numbers of TF-exposing microparticles above the 95th percentile, the cellular origin of these microparticles was studied by double labelling of the TF-exposing MP using flow cytometry. Chapter 7 studied the predictive value of the fibrin generation test for the development of VTE in a large cohort of cancer patients and compared it with previously studied biomarkers and a clinical prediction score. In this multicenter study more than 400 patients were included in 6 different hospitals, and patients were followed for 6 months to see whether they would develop VTE. In chapter 8 we investigated the effect of chemotherapy on microparticle composition and microparticle dependent coagulant activity in patients with non-small cell lung cancer and glioblastoma multiforme (brain cancer).

In the second part of this thesis the focus is on the diagnosis of VTE. In chapter 9 we summarized the current literature on the diagnosis of upper extremity DVT (UEDVT) in a Cochrane review. Chapter 10 describes the Armour study, a prospective multicenter management study in 400 patients with suspected UEDVT. All patients underwent a diagnostic algorithm consisting of the sequential application of a clinical decision score (Constans’ score), D-dimer testing and (repeated) ultrasonography and were followed for 3 months to assess the safety of the strategy. Finally, chapter 11 describes the limitations of screening for cancer using CT-scans in patients with idiopathic VTE.

In the third part of this thesis the management of VTE is addressed. In chapter 12 a survey assessed the current approach to the treatment of patients with cancer and VTE, in multiple countries and among different specialists. Chapter 13 investigated the real world treatment in 600 Dutch patients with cancer and pulmonary embolism and compared this to other patients with pulmonary embolism and no cancer.
REFERENCE LIST


Chapter 1


