Venous thromboembolism, coagulation and cancer
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Cancer patients have an increased risk of venous thromboembolism. For years this association was ascribed to Armand Trousseau who wrote in 1865 ‘L’expérience clinique m’a démontré toute la valeur sémiotique de la phlegmatia dans les cachexies cancéreuses en particulier’ [1]. However, a recent thorough literature search led to the finding that Jean-Baptiste Bouillaud (1796-1881) reported on this relationship forty years earlier [2]. This French physician described fibrin clots in the veins of three patients with cancer [3]. It was only in the 20th century that the first report on a patient with spontaneous venous thrombosis as a sign of an underlying occult cancer was published by Illtyd James [4]. Despite these early publications, the relationship between cancer and venous thrombosis was not intensively investigated until the early 1980’s. In the last two decades of the previous century until today research has focussed on at least three aspects of this association. The first is the precise mechanism(s) by which cancer cells are able to induce a hypercoagulable state and how this leads to an environment favourable for cancer growth. The second aspect is the potential inhibitory effect of anticoagulant drugs on cancer progression. Finally, a large amount of data has been collected on the high incidence of thrombotic complications in cancer patients.

Cancer cells can express several coagulation proteins, thereby activating the coagulation system at several levels. Tissue factor, the initiator of the coagulation system, is expressed by several cancer types [5-7]. Furthermore, chemokines, such as tumour necrosis factor α, are excreted by cancer cells and they can activate monocytes and macrophages, resulting in tissue factor expression on these cells [8]. Lower levels of activated protein C, a natural anticoagulant protein, are observed in cancer patients due to downregulation of thrombomodulin on the endothelial cells by these released chemokines, thereby further contributing to the hypercoagulable state [9]. In addition, cancer cells can express urokinase-type and tissue type plasminogen activators, plasminogen-activator inhibitor 1 and 2 and the plasminogen-activator receptor. The balance between these fibrinolytic proteins leads to an impaired fibrinolysis [10].

A more recent factor contributing to the hypercoagulable state in cancer patients are circulating microparticles. Different types of cells, including cancer cells and platelets, are able to form these cell membrane derived particles. Their phospholipid membrane can bind several coagulation factors. Particles derived from activated monocytes, endothelial and cancer cells can express tissue factor, making them procoagulant [11]. In cancer patients high levels of these microparticles have been associated with venous thrombosis and a worse prognosis [12;13].
By the formation of the end product of the coagulation system, fibrin, around the cancer cells angiogenesis is supported and the cancer cells are protected against immune attacks [14].

Also individual coagulation proteins, irrespective of their role in fibrin formation, create an environment favourable for cancer growth. Binding of FVIIa to the extra cellular domain of tissue factor increases the amount of intracellular calcium. This activates protein kinase C that in turn phosphorylates the cytoplasmic tail of tissue factor, which subsequently enhances cancer cell motility and migration and the production of growth factors [15]. Thrombin stimulates the expression of adhesion molecules on cancer cells and the production of chemokines by binding to protein activated receptors (PARs), members of the G-coupled receptors. Four PAR receptors have been described. PAR signalling increases cancer cell motility and survival and the production of growth factors. Thrombin mainly binds to PAR-1 and PAR-4, whereas other coagulation factors such as the TF-FVIIa complex and FXa can activate PAR-2. Furthermore, thrombin activates platelets by binding to their PAR-1 receptor [15]. The activated platelets express P-selectin, a ligand for the adhesion of cancer cells. A shield of platelets is formed and protects the cancer cell in the blood stream from the immune system. Also the expression of adhesion molecules on endothelial cells is upregulated by thrombin. Adhesion of the cancer cells to the activated platelets and the endothelium facilitates extravasation [16].

Finally, large amounts of growth factors are released by activated platelets, especially vascular endothelial growth factor. This hormone causes, next to its well-known angiogenic stimulating properties, leakage of plasma proteins through the vessel wall, including fibrinogen, creating again a proangiogenic environment [14].

The first clinical observation of an inhibitory effect on cancer growth of anticoagulants came from a study published in 1992 [17]. This trial compared the efficacy and safety of two types of heparin, low molecular weight heparin (LMWH) and unfractionated heparin (UFH), in the initial treatment of patients with venous thromboembolism. Unexpectedly, the subgroup of patients with venous thromboembolism and also cancer treated with LMWH for 5 to 10 days had a better survival after three months as compared to those receiving UFH. Two meta-analyses were performed including all venous thromboembolism-treatment studies and both confirmed this finding [18;19]. Hettiarachchi and colleagues observed a relative risk reduction for mortality after three months of 0.72 (95% CI 0.55-0.96) in the cancer patients treated with LMWH relative to
those who received UFH. Subsequently, clinical trials evaluating the effect of heparin on survival and disease progression in cancer patients without venous thromboembolism were performed. Sofar, in total six studies are available and only one convincingly demonstrated a survival advantage, although the other investigations support a potential benefit of LMWH [20-25]. However, many aspects of this clinical observation remain to be unravelled, including the underlying molecular mechanisms, the optimal dose and duration of the LMWH treatment and the cancer types in which the impairment of cancer growth by LMWH is the highest.

Venous thromboembolism is a common complication in cancer patients [26]. Approximately 5 to 10% of all cancer patients will develop a venous thromboembolism within the first year after diagnosis [27]. This high risk can be explained by several factors. First, the cancer itself causes a hypercoagulable state as discussed above, depending on tumour type and stage. But also stasis of blood, by the compression of vessels and immobilisation of the patient, enhances thrombus formation. Furthermore, anticancer therapy frequently has a procoagulant side effect. Chemotherapy, radiotherapy, surgery, but also the newer anti-hormonal and anti-angiogenesis agents are associated with an increased risk of venous thrombosis [28]. Despite the knowledge about all these risk factors and the relatively high absolute incidence, providing thromboprophylaxis in cancer patients is not generally recommended [29].

Another unresolved aspect in the association of cancer and venous thrombosis is the need for cancer screening in patients who present with idiopathic venous thrombosis. In approximately 10% of these patients cancer is diagnosed within the first year after diagnosis [30]. The type of cancer varies widely [31;32] and the highest odds ratios have been observed for pancreatic cancer, haematological malignancies and lung cancer [33]. The debate concentrates on whether a limited screening strategy, existing of a careful history taking, a thorough physical examination, basic laboratory testing and chest X ray, suffices, or that extensive screening with various imaging techniques is warranted [34;35].

Next to the established association of idiopathic deep vein thrombosis and pulmonary embolism with occult cancer, there is uncertainty whether patients presenting with an idiopathic superficial thrombophlebitis have an increased risk of cancer.
OUTLINE OF THE THESIS
This thesis consists of three parts. The first focuses on the effect of anticoagulant treatment in cancer patients with and without VTE. The second part addresses the association between venous thrombosis and the subsequent cancer risk, whereas the final part evaluates the significance of microparticles in cancer patients.

Chapter 2 reviews the two sided association of cancer and the coagulation system. The development of new anticoagulant drugs with special attention to their use in cancer patients is summarized in Chapter 3. In Chapter 4 a meta-analysis on the effect of heparins on cancer progression is presented, whereas in Chapters 5 and 6 the efficacy and safety of two new anticoagulant drugs, fondaparinux and idraparinux, are reported with a focus on those patients with venous thromboembolism and cancer. Chapter 7 discusses the first results of a large clinical trial in which patients with advanced cancer were randomized to LMWH (nadroparin) or no treatment. Overall survival and safety were the main outcomes.

The thesis continues with part two which begins with Chapter 8 that reports the results of the Trousseau study. This clinical study compares a limited cancer screening strategy to an extensive one in patients with idiopathic venous thromboembolism. The relative cost effectiveness of these two screening approaches is detailed in Chapter 9. The aim of Chapter 10 is to determine the incidence of cancer after a first episode of idiopathic superficial thrombophlebitis. The findings of a large cohort study in primary care are reported.

The last part deals with microparticles and concerns two chapters. In Chapter 11, the predictive value of procoagulant microparticles for the development of venous thromboembolism in cancer patients is investigated. Chapter 12 reviews the contribution of microparticles in cancer progression.
REFERENCES


Introduction


PART

Anticoagulant treatment in cancer patients