Cancer, thrombosis and low-molecular-weight heparins
Piccioli, A.

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CHAPTER 6

Venous thromboembolism as first manifestation of cancer.

Piccioli A, Prandoni P.

University Hospital of Padua, Italy

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Abstract

Since Trousseau's time numerous studies have addressed the relationship between cancer and venousthromboembolism (VTE) providing firm evidence of theincreased risk of subsequent clinically overt malignancy during the follow-up of patients with idiopathic VTE. These malignancies are not limited to certain subtypes, but involve virtually all body systems. This knowledge has led to a long-standing debate on the need to screen for occult malignancies patients with idiopathic VTE with no clinical evidence of cancer at the time of the index thrombotic event. 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 an answer to these questions. Since the first observation by Trousseau (1) in 1865 relating thrombotic phenomena to malignancy, numerous studies have addressed the relationship between malignant disease and venous thromboembolism (VTE). Cancer and VTE are connected by a two-way clinical correlation. In fact, an increased incidence of VTE in patients with known malignancy has been convincingly demonstrated. Post-mortem studies have shown a markedly increased incidence of thromboembolic disease in patients who died of cancer (2, 3). In cohort studies of surgical patients, the incidence of deep vein thrombosis (DVT) was markedly higher in patients with malignant disorders than in patients with other (non-malignant) diseases (4–9). Moreover, several studies, conducted over the past two decades among patients presenting with VTE have concluded that the incidence of subsequently diagnosed malignant neoplasms is high compared to the general population, and it is much higher in patients presenting with idiopathic than in patients with secondary VTE (10–29). The assessment of this strong association has led to a longstanding debate on whether to screen patients with a first episode of idiopathic VTE with no clinical complaint of underlying malignancy for malignant processes. The aim of the present article is to investigate this strong relationship by looking at its biological plausibility, to discuss whether occult cancer is more frequent in patients with VTE than in the general population, to assess the differences in the incidence between idiopathic and secondary VTE, to examine the most commonly found malignancies during the follow-up of these patients, and to discuss whether a systematic workup for detecting these hidden cancers is useful.

Biological Plausibility

Pathogenetic mechanisms accounting for the development of thrombotic disorders in cancer patients were described by Virchow more than a century ago. They include hypercoagulability due to tumour cell activation of clotting, vessel wall injuries and stasis. Under normal circumstances, prothrombotic and anticoagulant forces are perfectly balanced inside the blood system. Neoplastic cells are able to convert this homeostatic pattern into a prothrombotic state in two different ways. They can activate the clotting system directly by synthesizing and releasing procoagulants into the blood system. Best-characterized tumour cell procoagulant is tissue factor, which can activate the extrinsic pathway through interaction with factor VIII and factor X activators (30, 31); tissue factor procoagulant activity has been identified in some acute leukaemias (32) and in solid tumours of the ovary, stomach and kidney (33). Tumour cells can also activate directly factor X by procoagulantcysteine proteinase, which has been found in some patients with lung, prostate, colon, breast and kidney cancers as well as in patients with leukaemia (34, 35). Tumour cells can also activate the clotting system indirectly by stimulating mononuclear cells to synthesize and release various procoagulants (36–38). Along with tumour-associated procoagulants, the clotting system may be further perturbed either by therapeutic cancer interventions, which are started when the cancer is discovered, or by the peculiar ability of cancer cells to directly injure vascular endothelium (39, 40). Venous stasis, which is commonly caused by immobilization, venous obstruction, venous dilatation and increased blood viscosity, predisposes to VTE by preventing activated coagulation factors from being diluted and cleared by normal blood flow (41).
Patients with VTE and Their Risk of Cancer

To evaluate whether patients with VTE are at higher risk of developing cancer during follow-up when compared to the general population it is necessary to assess the difference in the frequency of newly diagnosed malignancies between these two populations (table 1). The incidence of newly diagnosed malignancies in patients with suspected VTE compared with that in patients in whom this diagnosis was excluded by normal objective diagnostic tests has been evaluated by Gore et al. (10) and Goldberget al. (13). As reported, the risk of a subsequent cancer was higher among the patient group (study group) as compared to subjects in whom the disease was ruled out (general population). Relative risks were higher in younger than in older patients. Conversely, other later studies failed to confirm this association (12, 20).

Recently, two large Scandinavian studies, based on national registrations of admissions and cancer diagnosis, have reported sound evidence of the consistency of the increased risk of harbouring a malignant disease after experiencing an episode of VTE (28, 29). In the study by Sorensen et al (28) the standardized incidence ratio for cancer in a cohort of 26,610 VTE patients from the Danish National Registry of patients was as high as 3.0 during the first 6-month period after discharge. Baronet al (29) assessed the cancer incidence consulting the Swedish Inpatient Register and the Swedish Cancer Registry. VTE was a clear marker of cancer risk since the standard incidence ratio for cancer was as high as 4.4 in VTE patients during the 1st year after discharge. The incidence of newly diagnosed cancers in these two studies was 2- to 4-fold higher than the expected incidence in a comparable population of the same age and gender, but without VTE. However, it must be considered that large population-based retrospective studies may have some limitations, as pointed out by Rickles and Levine in this issue.

Idiopathic versus Secondary VTE and Risk of Subsequent Cancer

In order to identify subgroups of VTE patients at higher risk of having an underlying malignancy, several studies have compared the subsequent development of cancer in patients with apparently idiopathic thrombosis versus those in whom the VTE event was secondary to a well-established risk factor. In these studies, the homogeneity of the study population was guaranteed by them having the same disease as the control patients, receiving the same treatment, and thus differing only as regards the presence or absence of a risk factor for VTE. In all studies, the risk of developing subsequent malignancy was much higher patients with idiopathic VTE than in patients with secondary VTE (table 2). The pooled odds ratio for newly diagnosed cancer in patients with idiopathic VTE compared to that in patients with secondary VTE was 4.81 (95% CI, 3.45–6.72). In addition, patients with recurrent VTE exhibited an even higher risk of developing subsequent cancer. The extension of DVT might also be considered a risk factor for occult cancer, as suggested by recent data demonstrating that in cancer patients with DVT the contralateral leg is more frequently involved than inpatients free from malignancy (26, 42).

Most Common Cancer Types

Although some of the studies comparing the frequency of underlying cancer in patients with idiopathic versus secondary DVT do not give information about cancer types, overall prostate and colorectal cancer have been the most commonly found. Other common sites were lung, pancreas, stomach and bladder. In the above-mentioned two large population-based studies pooled together (28,29), during the 1st year of follow-up after the thrombotic event 3,069 patients were diagnosed with cancer. Of these, prostate cancer was the most frequently occurring (13.5%) followed by cancer of the lung (10.5%), colon (8.6%), pancreas (7.3%) and stomach (5.9%). The frequency of 1st-year diagnosis of different types of cancer in the two cohorts of VTE patients pooled together is available in table 3. However, the two large population-based studies performed in Scandinavia might not necessarily reflect the
true distribution of cancer subtypes occurring in patients with thrombosis. Screening patients with idiopathic thromboembolism for specific cancers may be effective, but it is often insufficient, as a substantial number of patients with VTE will commonly develop other types of cancer that are potentially identifiable and treatable, i.e. uterus, breast, urinary tract and a variety of haematological disorders.

Is a Systemic Extensive Screening for Occult Malignancy Worthwhile?

Despite the conclusive evidence of a strong relationship between idiopathic VTE and the risk of hidden cancer, whether an extensive screening for occult malignancy in patients with idiopathic VTE is appropriate is still controversial. Monreal et al (15), applying an extensive screening which included erythrocyte sedimentation rate, whole blood cells counts, liver function tests, electrophoresis of serum protein, lactate dehydrogenase, carcinoembryogenicantigen (CEA) levels, chest X ray, abdominallultrasonography and computed tomography (CT), as well as an upper gastrointestinal endoscopy, diagnosed 6 new malignancies after screening 108 patients, most of them with idiopathic VTE. Three of these patients had signs or symptoms suggestive of the presence of the malignant process at the time of presentation for index DVT. Similarly Bastounis et al. (18) performed abdomino-pelvic CT and CEA levels in all their patients with DVT, and found 21 malignant processes in 86 patients with idiopathic VTE, who were otherwise healthy (18). Cornuz et al (21) in a retrospective follow-up study reported 16 malignancies identified among 136 patients hospitalized for idiopathic DVT. All 16 malignancies were diagnosed in 80 patients who had one or more abnormal findings at the initial clinical evaluation. No standardized, validated guidelines are currently available on this subject. The efficacy of a screening programme is based on the high incidence of the illness in the studied population and relies on the likelihood of an early diagnosis of treatable occult malignancies, therefore improving long-term survival. Since extensive screening procedures are both associated with high costs and also result in some morbidity, they are acceptable if they are cost-effective and have an impact on cancer-related mortality. To compare the strategy of extensive screening versus no further testing for occult malignant disease, we have recently conducted a multicentre randomized clinical trial in 201 apparently cancer-free patients with acute idiopathic venous thrombosis or pulmonary embolism (43). The primary outcome of the study was cancer-related mortality, while secondary outcomes were to assess the proportion of hidden malignancies detected at the presentation of the patients by a predefined schedule, and to compare the proportion of patients in the two study groups with objectively documented residual malignancy or recurrent malignancy at 24 months of follow-up. Patients with a first episode of idiopathic VTE, after negative initial routine battery tests, were randomized to undergo either an extensive screening or no further testing for malignancy. Patients allocated to the standard strategy were followed up as usual for the index thrombotic event leaving their attending physicians free to prescribe any test they considered worthwhile. Patients randomized to the extensive screening group were offered to undergo an ultrasound of the abdomen and pelvis, followed by CT of the abdomen and pelvis, gastroscopy or double contrast barium swallow, colonoscopy or sigmoidoscopy followed by barium enema, haem occult, sputum cytology and tumour markers including CEA, alpha-fetoprotein and CA125. These tests were extended with mammography and papsmear for women and with trans abdominal ultrasound of the prostate and specific prostatic antigen for men. All patients had their follow-up visits for the index thrombotic event at 3, 12 and 24 months. The study has now reached the stage of final data processing.
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