Risk factors of thrombosis in cancer : the role of microparticles

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4 Risk of venous thromboembolism in lung cancer

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Abstract

Purpose of review

To evaluate risk factors of venous thromboembolism (VTE) in lung cancer patients.

Recent findings

Calculated incidence rates of VTE in lung carcinoma patients vary from 40 to 100 cases per 1000 person-years, which is much higher than the estimated 1-2 cases per 1000 person-years of the general population. Patients with adenocarcinoma have a higher risk of VTE than patients with squamous cell lung carcinoma. The risk of VTE seems to be 2-fold higher in NSCLC than in SCLC patients.

Other risk factors of VTE are pneumonectomy, metastatic disease, the use of specific chemotherapeutic drugs in combination with novel targeted drugs, *e.g.* anti-angiogeneic agents (*e.g.* anti-vascular endothelial growth factor, VEGF) agents, and elevated pre-chemotherapy platelet counts.

Interestingly, tissue factor (TF), the initiator of the clotting cascade, may be (over) expressed in lung carcinoma cells. Active TF bearing microparticles (MP), which may originate from the tumour cells themselves, have been found in the circulation of cancer patients. MP-associated TF activity may provide a causative link between cancer and thrombosis and play a decisive role in the pathogenesis of the prothrombotic state in cancer patients.

Summary

Risk factors of VTE in lung cancer patients are adenocarcinoma, metastatic disease, pneumonectomy and anti-cancer therapy including chemotherapy and anti-VEGF targeted drugs. Other risk factors identified include pretreatment platelet counts and active TF-expressing circulating microparticles.

Introduction

Incidence and mortality risk of VTE in the general population are rare. The risk ratio of VTE in the general population is not precisely known and was estimated to be between 1–3 in 1000 per year (1;2). Recently, incidence and mortality of a first venous thrombosis was estimated in a general population of Norway (3). The incidence rate for all first venous thrombosis was 1.43 per 1000 person-years (95% CI: 1.33-1.54), for deep vein thrombosis it was 0.93 per 1000 person-years (95% CI: 0.85-1.02) and for pulmonary embolism it was 0.50 per 1000 person-years (95% CI: 0.44-0.56).The incidence rates increased markedly with age and were slightly higher in women than in men. The 30-day case-fatality was higher in patients with pulmonary embolism compared to those with deep vein thrombosis (9.7% *vs.* 4.6%, risk ratio 2.1 (95% CI: 1.2-3.7). It was much higher in patients with cancer compared to patients without (19.1% vs. 3.6%, risk ratio 3.8 (95% CI 1.6-9.2)). The risk of dying was highest in the first months subsequent to the venous thrombosis.

Known risk factors of thromboembolism are surgery, immobilization, the use of oral anticonceptives, and the presence of specific gene mutations in factor V Leiden and in the prothombine gene. More recently also lipid abnormalities have been suggested to contribute to the development of VTE Elevated triglyceride levels were associated with a doubling of risk of venous thrombosis in postmenopausal women, whereas elevated HDL cholesterol levels were associated with a decreased risk (4).

VTE and cancer

Thromboembolism is a well-recognized complication of malignant disease with a spectrum of clinical manifestations varying from venous thromboembolism (VTE) and Trousseau's syndrome to disseminated intravascular coagulation (5). The link between activation of the blood coagulation system and malignancy dates back to 1865 (6). Thereafter venous thrombosis has been reported to be a common complication in patients with malignancy (7;8), but although lung cancer is the second most common cancer in western countries and the leading cause of cancer death in men and women (9) strikingly few papers on the phenomenon of VTE in lung cancer patients are found and data on mortality due to VTE are limited.

Utilizing a Medicare database, Levitan et al found that the incidence of VTE is high among cancer patients, and lung cancer belonged to the group of malignancies with the highest incidence rates (10). More recently, the overall risk of venous thrombosis was found

to be 7-fold increased in patients with a malignancy versus persons without malignancy (11). Patients with haematological malignancies had the highest risk of venous thrombosis followed by lung cancer. The risk of venous thrombosis was highest in the first few months after the diagnosis of malignancy and in the presence of distant metastases. Cancer patients who were carriers of the factor V Leiden and prothrombin 20210A mutations, known risk factors to develop venous thrombosis, appeared to have an even higher risk (11).

Risk of VTE in different histological types of lung cancer and stages of the disease

Although lung cancer incidence has increased during the last decades and Non Small Cell Lung Cancer (NSCLC) accounts for approximately 80% of all lung tumours, few reports exist on the incidence of VTE in NSCLC. For small cell lung cancer (SCLC), which accounts for up to one-fifth of all lung cancers, even less reports exist on the risk of VTE.

The association between VTE and lung cancer has been reported more than twenty years ago (12;13). Recently, Blom *et al*. (14) investigated the thrombotic risk in 537 NSCLC patients and observed that the risk of VTE was 20-fold higher than in the general population (standardized morbidity ratio (SMR): 20.0 (14.6-27.4). Patients with adenocarcinoma of the lung had a 3-fold higher risk (incidence: 66.7 per 1000 years) than patients squamous cell carcinoma of the lung (incidence: 21.2 per 1000 years). In adeno- and squamous carcinoma together, they observed 39 events of VTE over 879 years of follow-up for an overall incidence of VTE of 44.4 per 1000 person-years. During chemotherapy or radiotherapy and in the presence of metastases the risk of VTE was even higher (14).

In the past, autopsy and retrospective studies had already indicated that various adenocarcinomas are most strongly associated with VTE (15;16) and this has led to the widespread belief that mucin-producing adenocarcinomas are indeed the most often tumours associated with VTE. The findings of Blom *et al*. (14) seem to support the notion that specific properties of adenocarcinomas are indeed responsible the observed increased thrombosis in adenocarcinoma patients.

According to data reported in abstract form at the American Thoracic Society International Conference of 2006, the overall incidence of VTE in lung cancer patients was even higher (17). For their analysis, the investigators determined the occurrence of an objectively defined VTE in 598 consecutive patients with a histologically confirmed diagnosis of lung cancer. Seventy-three (12.2%) patients developed a VTE for a total of

730 person-years, which translates into an incidence rate of 100 cases per 1,000 person years. Multivariate analysis indicated that patients with NSCLC were 2.1 times more likely than patients with SCLCS to develop VTE. Age, sex, stage of the lung cancer, ECOG performance, and recent surgery did not predict VTE. This study has not been reported yet as a peer-reviewed paper (17).

VTE as first sign of occult lung cancer

White *et al*. (18) used the California Cancer Registry to identify diagnosed cases of 19 common malignancies during a 6-year period. Cases were linked to a hospital discharge database to identify incident VTE events within 1 year before the cancer diagnosis date. Among 528,693 cancer cases, the incidence of preceding VTE was increased over that expected in the year preceding the diagnosis of cancer, but in particular only during the 4-month period immediately preceding the cancer diagnosis date ($P < .001$). Almost all of these unexpected VTE cases were associated with a diagnosis of metastatic-stage cancer with a standardized incidence ratio (SIR) of 2.3 (95% confidence interval, 2.0-2.6; $P < .001$). Only 7 cancer types were associated with a significantly elevated SIR: acute myelogenous leukaemia, non-Hodgkin lymphoma; and renal cell, ovarian, pancreatic, stomach, and lung cancer (SIR, range, 1.8-4.2).

Pathogenesis of cancer-related thrombosis

The development of VTE in cancer patients seems to be a multifactorial event involving several mechanisms, including inflammation due to necrosis or release of acute phase reactants and haemodynamic disorder, such as stasis. Tumour-specific mechanisms may result in down-regulation of anticoagulant and an up-regulation of procoagulant proteins, which might contribute to the general hypercoagulable condition of cancer patients (19). Cancer cells themselves may produce a number of procoagulant substances including tissue factor (TF), the initiator of the clotting cascade as for instance reported by Yu *et al*. (20). Few studies have attempted to correlate the haemostatic abnormalities in cancer patients with the clinical event of VTE, but so far -with the exception of a small study by Falanga *et al*. (21), in which preoperative thrombin-antithrombin complex levels correlated with the risk of postoperative VTE in cancer patients- no significant difference in clotting factor profile has been found to distinguish cancer patients who did develop VTE from those who did not. Importantly, to our knowledge extensive studies of hypercoagulability in malignancy have not successfully demonstrated a specific coagulation abnormality in cancer patients which predicts for development of VTE.

Tissue factor, microparticles and VTE

Importantly, lung cancer, in particular NSCLC, has been shown to express tissue factor; Callander *et al*. (22) indeed showed that lung cancer expresses TF, but Ornstein et al (23) reported that lung carcinomas (both squamous cell and adenocarcinoma) rarely and inconsistently expressed TF. More recently Sawada *et al*. (24) showed that NSCLC cells produce various amounts of TF but they did not determine the functional activity of the TF. This information is critically important, as only active and not inactive TF is able to initiate coagulation. The activation state of membrane-bound TF depends on the conformational state of TF which is determined by the presence or absence of a specific disulfide bond.

Sato *et al*. (25) reported Trousseau's syndrome in a patient with an adenocarcinoma of the lung in which TF seemed to play a pivotal role in the pathogenesis of recurrent VTE. In their case a markedly elevated plasma TF level was found. Furthermore, cancer cells were shown to express tissue factor as demonstrated by staining of tumour tissue with an anti-tissue factor monoclonal antibody, suggesting that TF in the circulation was released by the lung carcinoma cells.

Tesselaar *et al*. (26) investigated the association between clinically manifest VTE and procoagulant properties of circulating microparticles (MP) isolated from blood of unselected pancreas and breast adenocarcinoma patients, of whom a number presented with ultrasound or CT-scan confirmed VTE. They showed that elevated MP-associated TF activity significantly correlated with development of VTE in cancer patients with disseminated mucinous carcinomas. They also investigated individuals (without cancer) who presented with VTE, in one of these subjects who presented with idiopathic VTE of both legs, a highly elevated MP-associated TF activity was found. Strikingly, within one month following presentation with bilateral deep venous thrombosis, this patient was being diagnosed with a disseminated mucinous adenocarcinoma of the lung. Their findings suggest that the presence of active TF-bearing MP in the circulation of individuals who present with VTE may indicate the presence of an occult adenocarcinoma. Whether MP-associated TF activity indeed predicts the presence of occult adenocarcinomas will now be investigated by them in a prospective cohort study.

Interestingly, Del Conde *et al*. (27) reported a patient with a giant-cell lung carcinoma with a severe form of Trousseau's syndrome, who -despite receiving potent antithrombotic therapy- suffered eleven major arterial and venous thrombotic events over a 5 month period. This patient had a 41-fold higher concentration of plasma tissue factor

as compared to the mean plasma TF concentration examined in 16 normal individuals. Tumour cells from a lymph node stained intensely for TF. Microvesicles derived from patient plasma were found to express TF, and these cell-derived MP may have been shed by the cancer cells.

VTE and surgery in lung cancer patients

Cancer patients undergoing surgery have at least twice the risk of postoperative deep venous thrombosis and were known to have a more than 3-fold increased risk of fatal pulmonary embolism than non-cancer patients undergoing similar procedures (28). Interestingly, mortality due to VTE has been reported to occur predominantly in patients with squamous cell lung carcinoma following surgery (29). Patients with cancer are also more likely to develop VTE post-operatively despite thrombosis prophylaxis (30;31). After surgery, both pneumonectomy and lobectomy, pulmonary vein thrombosis has been shown to occur (32). Compared to patients who undergo surgery for other reasons than lung malignancies, *e.g.* orthopaedic or gynaecological operations, patients who undergo thoracic surgery seem to have a lower risk of VTE (33) This seemingly contradiction could be explained by the high risk for other severe of even fatal complication following pneumonectomy compared to other types of operations, which may result in an underestimation of the risk of VTE. .

Pulmonary embolism is the second cause of mortality after pneumonectomy for a malignancy and such patients have the highest risk to die from pulmonary embolism (29).

In a more recent published study of Mason *et al.* (34) the incidence of postoperative VTE after pneumectomy for malignancies was higher (7.4 %) as compared to that reported in older literature with a peak incidence within 7 days after the operation. Most patients had already been discharged from the hospital. Higher pack-years of smoking were associated with increased risk, as well as with earlier occurrence of VTE. Patients with VTE had a poor survival compared to patients who did not and this was valid for upper- as well as for lower extremities thrombosis. The difference in survival persisted after censoring for deaths directly attributable to venous thromboembolism. Based on these findings, VTE is a frequent event after pneumonectomy, and improved prophylaxis in high risk patients may prevent morbidity and mortality after pneumonectomy for lung malignancy and improve the poor survival outcome in these patients.

VTE in lung cancer patients undergoing chemotherapy and treatment with novel targeted drugs

Combined chemotherapy (either in combination with radiotherapy) is the current standard treatment for advanced stage NSCLC as well as in the treatment of SCLC patients and VTE is a well known complication of anticancer therapy (35-37). Since chemotherapy increases the risk of thrombosis in cancer patients (38), VTE may well become an important clinical issue in the general practice of physicians who treat lung cancer patients.

In SCLC high response rates are achieved by chemotherapy, but long-term outcome is still poor due to the majority of patients relapsing. This has resulted in the exploration of a number of new agents and novel strategies for the treatment of small-cell lung cancer, but with little benefit for the patient thus far.

Recommended first-line treatment in patients with advanced non-small-cell lung cancer (NSCLC) is chemotherapy with combinations of cisplatin plus gemcitabine, vinorelbine, or taxanes, with or without targeted therapy. Numico *et al*. (39) prospectively assessed the occurrence of VTE in patients with NSCLC who were treated consecutively with cisplatin and gemcitabine. They observed 22 VTE in 19 of 108 stage II-IV NSCLC patients who underwent chemotherapy (17.6%; 95% confidence interval [95% CI], 10.3-24.8%). A second thrombotic event was observed in patients who were given further chemotherapy after resolution of the first event, underscoring that indeed chemotherapy contributed to or even caused the thrombotic event.

Khorana *et al*. (40) analyzed data from a prospective, multicentre study in 3003 patients treated with at least one cycle of chemotherapy. VTE occurred in 58 (1.93%) over a median follow-up of 2.4 months (0.8%/month). The incidence varied significantly by site of cancer (P = 0.01) with highest rates in upper gastrointestinal (2.3%/month) and lung cancer (1.2%/month). Interestingly, an elevated pre-chemotherapy platelet count was associated with a 3-fold increased rate of VTE. In multivariate analysis, elevated pre-chemotherapy platelet count, site of cancer, haemoglobin <10 g/dL or use of erythropoietin, and use of white cell growth factors in high-risk sites of cancer were significantly associated with VTE. Their findings suggest that thrombosis prophylaxis should be considered in lung cancer patients undergoing chemotherapy who have elevated pre-chemotherapy platelet counts. Zecchina G, *et al*. (37) observed that thrombotic risk was further potentiated by chemotherapy in 49 unresectable, locally advanced, or metastatic lung cancer. In accordance with the literature in patients with other types of cancer, no alterations of coagulation inhibitors or activation of disseminated intravascular

coagulopathy and/or fibrinolysis as factors that induce chemotherapy-related thrombosis in lung cancer were found. Their findings also suggested that thrombocytosis played a role in triggering thrombotic complications.

Because combination chemotherapy schedules have induced higher better response rates than single agent chemotherapy, but did not result in major improvement of survival in NSCLC patients, many new drugs and drug combinations are currently under investigation. These include targeted therapies with epidermal growth factor receptor (EGFR) inhibitors, such as gefitinib and erlotinib, are effective in advanced NSCLC patients after first-line chemotherapy. Also VEGF-targeted inhibitory agents (inhibitors of vascular endothelial growth factor [VEGF] and its receptors) are currently being investigated for the treatment of NSCLC. A phase III study proved a significant benefit when bevacizumab was added to first-line chemotherapy in advanced NSCLC (41) and phase III clinical trials are currently in progress to investigate the efficacy of dual VEGF/EGFR inhibition, alone or in combination with chemotherapy, in patients with NSCLC. Clinical trials have shown that the use of anti-angiogenic agents is associated with an increase in incidence of VTE, but also haemorrhages. In the first reported phase I study of combined treatment with SU5416 plus gemcitabine-cisplatin more than 20% of the patients developed VTE (42). Combined modality treatment consisting of chemotherapy, radiotherapy and the antiangiogenic agent thalidomide in advanced NSCLC resulted in excessive toxicities with major thrombotic events (43), similar to what has been reported in other malignancies. Yoon *et al*. (44) reported that chemotherapy with bevacizumab, irinotecan, 5-fluorouracil and leucovorin was found to be associated with a large, embolizing thrombus in the thoracic aorta.

Behrendt *et al*. (45) conducted a retrospective cohort study in 1023 patients with stage IIIB, IV, or recurrent non-small cell lung cancer (NSCLC) who were followed during 2 randomized, double-blind trials of prinomastat versus placebo, plus gemcitabine/cisplatin (GC) or paclitaxel/carboplatin (PC). VTE included deep venous thrombosis (DVT) or pulmonary embolism (PE) confirmed by imaging or autopsy. The use of these novel matrix metalloproteinase inhibitor prinomastat in combination with chemotherapy, but not alone, resulted in approximate doubling of the risk of VTE in advanced NSLC patients.

Also in a large Phase III study in previously untreated stage IIIB/IV NSCLC patients who were treated with chemotherapy, with or without aprinocarsen, a new antisense oligonucleotide directed against protein kinase C-alpha, VTE was significantly increased in the experimental arm (46).

Thus, since the use of anti-angiogenic agents is associated with a marked increase in thromboembolic events, the clinician should be alert to the occurrence of such vascular complications. However, since some of these compounds may be associated with bleeding as well as with VTE, preventive measures are not easy to implement.

Another factor that nowadays may increase the risk of VTE in lung cancer patients is the recommended use of eythropoietin which has been shown to improve anaemia in cancer patients undergoing chemotherapy. Various trials reported the increased risk of thrombotic events following the use of eythropoietin indicating that the widespread use of eythropoietin should be cautioned

In conclusion

Lung cancer patients are at increased risk for VTE, and the life expectancy of a cancer patient with thrombosis is poor compared to a cancer patient without VTE. This supports the hypothesis that a local or systemic hypercoagulability state confers a growth advantage to tumour cells, while characteristics of individual patients' tumour cells may at the same time determine the tendency to develop thrombotic events. Risk factors for VTE are adenocarcinoma, NSCLC in comparison to SCLC, pneumonectomy, distant metastases and chemotherapy either alone or in combination with novel anti-angiogenic targeted drugs.

Abnormal coagulation profiles do not correlate with the development of thrombosis and are thus not useful to determine. The mechanism by which cancer predispose to thrombosis is still a challenging subject for research and a matter of controversies among researchers. One newly recognized mechanism by which cancer leads to thrombosis is microparticle-associated active tissue factor, which may be derived from various cells of the body, including the tumour cells themselves.

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