Thrombotic complications – prevention and treatment of venous thromboembolism in cancer patients

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Abstract

Patients with cancer have an increased risk of venous thromboembolism (VTE). There is evidence that the absolute risk of VTE in cancer patients depends on the type of cancer, stage of disease, treatment with chemotherapy, hormone therapy, immunomodulatory drugs (IMiDs), surgical procedures, the presence of an indwelling central venous catheter (CVC), age, immobilisation and length of anaesthesia. In these patients, risk factors may interact. In addition, cancer patients are at higher risk of recurrent VTE and bleeding than patients without cancer. Thrombotic complications have a significant impact on morbidity and, in some cases, also on mortality of patients with cancer; therefore, thromboprophylaxis to prevent VTE is needed. In some patients, venous thromboembolism may be the earliest symptom of an occult neoplasm. Furthermore, many patients who received a diagnosis of cancer within a year of VTE, already had distant metastases at the time of cancer diagnosis. The literature about the relation between cancer and venous thromboembolism was reviewed, with particular attention to risk factors of VTE in oncological patients, and connections between VTE and diagnosis of occult malignancy. Next, the prevention and treatment of venous thromboembolism in cancer patients is discussed. Finally, a potential anti-tumour and antimetastatic effect of anticoagulation and prognosis of these patients is described. Identifying high risk patients and the application of suitable prevention is the best way to reduce the incidence of VTE and its associated complications.

Key words

venous thromboembolism, cancer, anticoagulation

INTRODUCTION

Cancer is a principal pathology leading to the development of venous thromboembolism (VTE), both deep venous thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism (VTE) is one of the major causes of morbidity and mortality in cancer patients [1]. In patients with a first episode of apparently idiopathic thrombosis, 20% are discovered to already have a malignancy, and in up to 34% a new cancer will be diagnosed within one year [2]. The relative risk of developing VTE is approximately seven times higher in patients with active cancer [3]. Active cancer accounts for almost 20% of all new VTE events occurring in society [4]. Cancer patients are at four to sevenfold higher risk of venous thromboembolism (VTE) than patients without cancer [5]. According to researchers, the probability of death was highest for patients with concurrent venous thrombosis or pulmonary embolism and malignant disease, compared with those with either malignancy or VTE alone [6]. The likelihood of venous thromboembolism (VTE) in haematological diseases was less than in solid tumours. However, more recent reports suggest that the incidence of thromboembolic events in oncohematologic diseases may even be similar to that found in solid tumours.

Cancer patients also suffer from haemorrhage in the case of thrombocytes fluctuations [7]. Patients with the highest 1-year incidence rate of VTE are those with advanced-disease of the brain, lung, uterus, bladder, pancreas, stomach, and kidney. While receiving chemotherapy, cancer patients have a sevenfold higher risk to develop VTE, compared to other patients without cancer [8]. In addition, cancer patients are at threefold higher risk of recurrent VTE and twofold higher risk of bleeding than patients without cancer [5].

There is a very strong connection between the presence of cancer and the acute development of VTE [3]. Additionally, cancer patients are at threefold higher risk of recurrent VTE and twofold higher risk of bleeding than patients without cancer [5].

Risk factors of VTE in cancer patients. The total risk depends on cancer type, stage of disease, administration of chemotherapy, hormone therapy [8], immunomodulatory drugs (IMiDs) [7], surgical procedures, the presence of an indwelling central venous catheter, age, immobilisation, length of anaesthesia and reccurent VTE [8]. Chemotherapy and radiation increase the risk of venous thromboembolism [9, 10], besides which the risk factors may interact [9].

Virchow described that the occurrence of thromboses depends on the disturbance of the 'triad': correct blood composition, intact vessel wall and adequate blood fluidity. In oncological patients, this can occur in various ways: cancer induces procoagulant changes, both direct (thrombin generation) and indirect pathways [11].

Overall, the pathophysiology of therapy-associated with hypercoagulability seems to be a complex phenomenon that includes immobilisation, surgery-associated risk, vessel damage through chemotherapeutic agents, increased levels of procoagulant proteins, reduction of natural anticoagulants (protein C, protein S, antithrombin), suppression of fibrinolytic activity, increased platelet reactivity and activation, enhanced adhesion of neutrophils, down-regulation of thrombomodulin or direct release of procoagulants and cytokines from tumour cells [11].

The hypercoagulable condition in leukemia derives from the development of disseminated intravascular coagulation and thrombin generation as a result of the presence of a high level of circulating leukemic blasts, which have been shown to express tissue factor and release cancer procoagulant from their granular fractions [7].

There is a high risk of recurrent VTE in cancer patients. In a prospective clinical trial 20.7% of cancer patients suffered from recurrent thromboembolism, compared with 6.8% of patients without cancer. Patients with lung cancer or previous episodes of VTE were at higher risk for recurrent thromboembolism, while patients with breast cancer and stage I disease were at lower risk. Factors which need to be considered in the management of cancer patients with recurrent VTE are: subtherapeutic anticoagulation, extrinsic compression/venous stasis by tumour, nodal masses, Trousseau's syndrome, heparin-induced thrombocytopenia and rarely antiphospholipid syndrome [5]. Trousseau's syndrome is a cancer-associated hypercoagulable disorder named after the renowned 19th century French physician, Armand Trousseau. It is characterized by warfarin resistance, recurrent superficial thrombophlebitis, both arterial and venous thromboembolism, disseminated intravascular coagulation (DIC) and non-bacterial thrombotic endocarditis. Low molecular weight (LMWH) or unfractionated heparin (UFH) and possibly fondaparinux are required for successful control of this coagulopathy [5].

VTE and occult malignancy. VTE is a frequent complication of cancer and may be the earliest symptom of an occult neoplasm [12]. The incidence of cancer in patients with a primary diagnosis of VTE is reported to range from 7% in the first 6 months to 2 years after detection of VTE, to as high as 34% over 5 years. Furthermore, 40% of patients who received a diagnosis of cancer within a year of VTE already had distant metastases at the time of cancer diagnosis. There were also strong connections between VTE and a diagnosis of cancer of the pancreas, ovary, liver, and brain [6].

Large clinical trial – Screening for Occult Malignancy in Patients with Symptomatic Idiopathic Venous Thromboembolism (SOMIT) [13] demonstrated the efficiency of screening in detecting occult cancers. No significant difference was observed in the survival rate.

To date, without definitive data to demonstrate an advantage in terms of overall survival, using invasive diagnostic tests and intensive follow-up, patients should undergo only physical examination, occult faecal blood test, chest X-ray, urological visit in men, and gynaecological visit in women. The request for more expensive tests, such as computer tomography (CT) scan, digestive endoscopy, or tumour markers, should be carried out in the case of a strong clinical suspicion of occult cancer [8].

Prevention of VTE in cancer patients. A review of cancer patients who underwent surgery showed that they had double the risk of postoperative deep venous thrombosis than non-oncological patients who underwent similar procedures [14].

In cancer patients undergoing major cancer surgery, prophylaxis is recommended with low-molecular weight heparins (LMWH) once daily, e.g. Enoxaparin 4,000 units of anti-Xa activity, Dalteparin 5,000 units of anti-Xa activity, or unfractionated heparin (UFH) at 5,000 units three times daily. Mechanical methods, such as pneumatic calf compression, may be used with pharmacologic prophylaxis, but should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated because of active bleeding [8].

Randomised clinical trials investigated the efficacy and safety of LMWH vs. UFH for the prophylaxis of venous thromboembolism in patients with cancer [15, 16, 17, 18].

For patients who are treated by laparotomy, laparoscopy, thoracotomy or thoracoscopy lasting more than 30 minutes, LMWH should be considered for at least 10 days post-operatively [8].

Two clinical trials have demonstrated that in cancer patients undergoing elective major abdominal or pelvic surgery should receive both in-hospital and post-discharge prophylaxis with LMWH for up to one month after surgery. The risk of VTE in cancer patient was decreased by 60%, without significant bleeding complications [19, 20].

Clinical trials in hospitalized patients, which included cancer patients, have demonstrated that prevention leads to a lower VTE incidence compared with placebo, without increasing major bleeding [8].

Prophylaxis with UFH, LMWH or fondaparinux in hospitalized cancer immobilized patients with an acute medical complication is recommended [8].

Randomized trials have demonstrated the efficacy of 1 mg/daily treatment of warfarin, and of once daily 2,500 anti-Xa IU of a LMWH (dalteparin) in reducing the incidence of upper deep vein thrombosis in cancer patients with indwelling central venous catheters [21].

Extensive, routine prevention for advanced cancer patients receiving chemotherapy, in cancer patients receiving adjuvant, both chemotherapy and hormone therapy to prevent CVC-related VTE is not recommended [22], because of high (28%) risk of symptomatic VTE in these patients [23].

In the case of ambulatory multiple myeloma, patients treated with thalidomide or lenalidomide in combination with dexamethasone or chemotherapy, the guidelines by both the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) recommend prophylaxis with low molecular weight heparin (LMWH) or adjusted-dose warfarin (INR 2–3) [7].

Treatment of VTE in cancer patients. The main therapeutic options for long-term therapy for VTE in cancer patients are LMWH and vitamin K antagonists (VKA), such as warfarin. Fondaparinux has been used for chronic therapy of VTE in a limited number of cancer patients. Prospective studies have noted that cancer patients receiving VKA are threefold more likely to sufferer current VTE and twice as likely to bleed than non-cancer patients [5]. Clinical trials have demonstrated that using LMWH, compared to warfarin, the risk of recurrent VTE in cancer patient was reduced by 50%, with few bleeding complications [24].

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Randomised clinical trials demonstrate that in these patients long-term treatment for 6 months with 75–80% (i.e., 150 U/kg o.d.) of the initial dose of LMWH is safe and more effective than treatment with VKA. This scheme is recommended for long-term anticoagulant therapy in cancer patients [8].

Continuation of anticoagulant therapy is recommended for as long as there is clinical evidence of active cancer (e.g. chronic metastatic disease) [22].

Patients adequately anticoagulated who develop VTE recurrence should be examined for progression of their cancer. Oncological patients have a threefold higher risk of recurrent VTE and a threefold to sixfold higher risk of major bleeding while receiving anticoagulant treatment with a vitamin K antagonist (VKA), compared with non-cancer patients [8].

Patients on long-term anticoagulation with VKA who develop VTE when INR is in the sub-therapeutic range, can be retreated with UFH or LMWH until VKA anticoagulation achieves a stable INR between 2.0- 3.0. If there is recurrent VTE while the INR is in the therapeutic range there are two options for anticoagulation: 1) subcutaneous UFH maintaining a therapeutic aPTT (aPTT ratio from 1.5-2.5), or 2) LMWH at a weight-adjusted dose, and increase in the INR (to a target of 3.5). Full-dose LMWH (200 U/kg o.d.) can be resumed in patients with a VTE recurrence while receiving a reduced dose of LMWH or VKA anticoagulation as a long-term therapy. Increasing the dose of low molecular weight heparin results in a second recurrent VTE rate of 9%, it is well tolerated and without significant bleeding complications [8].

Heparin-induced thrombocytopenia (HIT) should be considered in any recently discharged cancer patient with both low molecular weight and unfractionated heparin exposure who presents with recurrent thromboembolism, particularly in association with a reduced platelet count. In cancer patients with HIT, fondaparinux has been used for chronic therapy of VTE [24].

A vena cava filter should be considered in patients with recurrent pulmonary embolism despite adequate anticoagulant treatment, or with a contraindication to active bleeding or profound, prolonged thrombocytopenia. The risk of bleeding is reduced, patients with a vena cava filter should receive or resume anticoagulant therapy in order to reduce the risk of recurrent deep vein thrombosis of the lower extremities [8].

Anticoagulation and prognosis of cancer patients. Based on long-term follow-up data on patients with thrombosis, oncological patients have a fourfold to eightfold higher risk of dying, compared with non-cancer patients, after an acute thromboembolic event. Clinical trials showed that one-year survival for patients with VTE was 12% compared to 36% in control patients. The mortality index associated with VTE was 2.2 for the one-year follow-up period. The higher mortality rate in patients with VTE may indicate that VTE is a marker of aggressive malignancies, or that these patients are more likely to die from thrombotic complications. In the trial, 40% of the patients were dead within 6 months and 57% were dead within one year. Of those with metastatic disease and VTE, only 30% were still alive a year later [25].

Scientists have described a potential anti-tumour and antimetastatic effect of low molecular weight heparin. This was due to the observation that death rates were lower when cancer patients with VTE received LMWH, rather than UFH. This observation, suggesting that the use of low molecular weight heparin improves tumour response and survival, has been confirmed in various settings with different cancer types and stages. LMWH therapy has also been shown to be safe for outpatient treatment for cancer. Further approaches to use LMWH as an adjunctive therapy to other anti-tumour therapies are underway [11].

CONCLUSION

Patients with cancer have a higher risk of VTE, recurrent VTE and its associated complications. Recent evidence from clinical trials shows that prevention and treatment with low molecular weight heparin may be advantageous for these patients.

Identifying high risk patients and the application of suitable prophylactic measure is the best way to decrease the incidence of VTE and its associated complications. Further research is warranted to study the potential anti-tumour or the antimetastatic effects of low molecular weight heparin, which may help to improve the prognosis of cancer patients.

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