INTRODUCTION

The European Society of Medical Oncology describes venous thromboembolism (VTE) as 'one of the most important causes of morbidity and mortality in cancer patients'[1]. Venous thromboembolism is a common and serious complication in patients with cancer and the second most frequent cause of death in this patient group.[2,3]

It is estimated that up to 1 in 5 cancer patients experience venous thrombosis,[4] and cancer patients with VTE have, on average, a 2.2-fold increase in mortality as compared to cancer patients without VTE.[5] The association between cancer and venous thromboembolism, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been widely acknowledged for almost two centuries. It was first recognised by Bouillard in 1823 and later described by Trousseau in 1844; the latter suggested that cancer was associated with "a special crisis of the blood which, irrespective of inflammation, favours intravenous coagulation". Trousseau was also the first to register a significant connection between DVT occurrence and a yet undiagnosed or 'occult' cancer – an observation that has been upheld in subsequent research over the decades.

Clinical association

Since the time of Bouillard and Trousseau, multiple studies have confirmed the two-way clinical association between cancer and thrombosis. Research has established that cancer is a prothrombotic disease, with patients at an elevated risk for VTE, particularly during the first few months after diagnosis and in the presence of distant metastases,[6] and, conversely, the risk for cancer seems elevated for at least two years after a first episode of idiopathic VTE.[7] Cancer is associated with a number of internal and external factors that increase risk for thrombosis. Perhaps the oldest and most dominant theory of the pathophysiology of thrombosis is that presented by Rudolf Virchow almost 160 years ago.[8] Based on pathologic observations, Virchow postulated that vascular obstruction was precipitated by, and thrombosis resulted from, three interrelated factors: "decreased blood flow" (venous stasis), "inflammation of or near the blood vessels" (vascular endothelial injury/dysfunction), and "intrinsic alterations in the nature of the blood itself" (hypercoagulability).

Virchow's Triad

These three separate but overlapping elements are the major factors responsible for the development of VTE. Each of these factors can form a clot on its own; however, the risk for thrombosis dramatically increases when two or three variables are in effect at the same time. This theory became known as “Virchow’s Triad”. Since that time, the role of each of these elements of the triad have been extensively evaluated, and it is clear that essentially all prothrombotic factors - systemic and molecular - influence at least one of these three mechanisms. Cancer appears to dramatically increase the risk for VTE through direct and indirect influences on each element of Virchow’s triad. The impact of cancer and its treatment can be observed clearly on each of the three “pillars” of Virchow’s Triad:

Click the different sections of the animation to see more:

Venous stasis:

- Increased blood viscosity
- Mechanical blockage (tumour extrinsic compression or invasion)
- Patient immobility due to cancer complications or treatment

Injury to a vessel wall

- Mechanical endothelial trauma (due to cancer invasion or treatment)
- Endothelial dysfunction/loss of anti-thrombotic properties
- Angiogenic stimuli

Hypercoagulability

- Increase in procoagulant activities
- Decrease in anticoagulant activities
- Increase in overall platelet activity
- Decrease in fibrinolytic activity

It is recognised that a direct link exists between the haemostatic system and cancer biology. Cancer growth itself is associated with the development of a hypercoagulable state. A unique feature in cancer is the role played by the expression of tumour cell-associated clot promoting properties. These properties lead to the activation of the clotting cascade, with the generation of thrombin and fibrin, and the stimulation of platelets, leukocytes and endothelial cells which expose their cellular procoagulant features.[9] Conversely, a number of these mechanisms can also contribute to tumour development and progression.[10]

Extrinsic factors

Compounding the underlying pathophysiologic propensity for coagulation, patients with cancer may also have a number of extrinsic factors that increase the thrombotic risk. These include surgery, anti-cancer therapies (chemotherapeutic and antiangiogenic agents), hormonal therapy, long-term immobilisation, central venous catheters, cancer type, advanced

disease stage, and old age. Chemotherapy is one of the most important risk factors for increased risk of VTE. A large US study found that the overall incidence of VTE in patients receiving chemotherapy was 7.3% after 3.5 months of treatment, rising to 13.5% at 12 months. The highest VTE risk was identified in patients with pancreatic, stomach, and lung cancer. [11]

Complications of CAT

Among survivors, complications commonly include recurrent VTE and post-thrombotic syndrome, which have a profound impact on the patient's quality of life. Timely and accurate diagnosis, and indeed prevention, of venous thromboembolism in cancer patients is imperative due to the unacceptable morbidity and mortality associated with a misdiagnosis. Landmark studies have demonstrated effective treatment of VTE reduced morbidity and increased survival. Low-molecular-weight heparin (LMWH) is preferred as an effective and safe means for prophylaxis and treatment of VTE. It has largely replaced unfractionated heparin and vitamin K antagonists. The advantages of LMWH include increased survival and quality of life, decreased rate of VTE, and low incidence of thrombocytopenia.[13] To help clinicians in the prevention and management of thrombotic events in cancer patients, a number of guidelines have been released from international scientific societies.[14,15] Prophylaxis is recommended in hospitalised cancer patients and patients undergoing major surgery. Treatment with LMWH should be considered as the first line of therapy for established VTE and to prevent recurrent thrombosis in patients with cancer.

References

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