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Cancer associated thrombosis and bleeding

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Abstract

Development of thrombosis is closely associated with poor prognosis in cancer patients. Cancer patients often fulfill Virchow's triad of hyper-coagulable state, vascular endothelial injury, and venous stasis. Cancer cells aberrantly express a variety of procoagulant factors, including tissue factor and podoplanin. Chemotherapeutic agents and radiation cause vascular endothelial injury, and reduced daily activity and bed rest for chemotherapy lead to venous stasis. Due to these factors, cancer patients are at high risk of developing thrombosis. Cancer patients are also at high risk of bleeding when they have disseminated intravascular coagulation and/or chemotherapy-induced thrombocytopenia as complications. International societies, such as the American Society of Clinical Oncology and the International Initiative on Thrombosis and Cancer (ITAC), have published clinical guidelines to help physicians better manage cancer-associated thrombosis (CAT). These guidelines recommend use of low molecular weight heparin or direct oral anticoagulants for the prevention of CAT, but unfortunately use of these drugs is not approved in Japan. This gap between Japan and other countries needs to be closed.

Keywords Cancer-associated thrombosis · Bleeding · Virchow's triad · Tissue factor · Podoplanin

Overview

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary embolism (PE). A Japanese VTE registry of 3027 consecutive patients with acute symptomatic VTE identified cancer as a risk factor for VTE [1]. In addition, the incidence of VTE in cancer patients is 4 to 7 times higher than in the general population [2, 3]. Thrombus formation is explained by Virchow's triad: venous stasis, vascular hyper-coagulable state, and vascular endothelial injury (Fig. 1). Cancer patients, especially those with advanced cancer, often fulfill Virchow's triad. As the cancer progresses, primary tumors and/or metastatic lymph nodes may compress vessels, thereby impairing blood flow. Bed rest for chemotherapy and reduced daily activity lead to venous stasis. Cancer cells aberrantly express a variety of procoagulant factors, including tissue factor (TF). These malignant cells also produce and release TF-expressing micro-vesicles that activate the coagulation cascade, leading to the formation of fibrin clots [4]. Podoplanin (PDPN) is also produced by cancer cells. PDPN binds to C-type lectin-like receptor 2 on platelets and activates platelets, leading to platelet aggregation and thrombocytopenia [5]. Some cancers cause an increase in neutrophils. Activated neutrophils release extracellular traps (NETs), which activate both the intrinsic coagulation cascade and platelets [6]. Catheter placement can cause vascular endothelial injury. The catheter itself activates the intrinsic coagulation cascade leading to clot formation. Chemotherapeutic agents such as cisplatin are known to cause vascular endothelial injury. In addition, recently introduced molecularly targeted agents such as ABL tyrosine kinase inhibitors for chronic myeloid leukemia may cause endothelial injury through off-target effects [7].

Cancer patients are prone to not only VTE, but also arterial thrombosis (e.g., myocardial infarction), which can adversely affect their quality of life (QOL) and survival. Importantly, thrombotic events are the second leading cause of death in cancer patients after cancer progression. Therefore, prevention of cancer-associated thrombosis (CAT) is crucial to improve the survival of cancer patients. International societies, including the American Society of Clinical Oncology and the International Society on Thrombosis and Haemostasis, have published clinical guidelines

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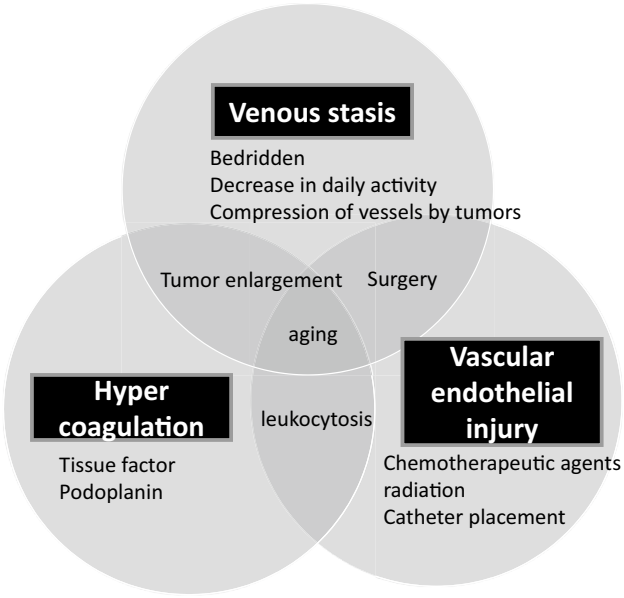

Fig. 1 Virchow's triad in cancer patients. As cancer progresses, cancer cells aberrantly express procoagulant factors, including tissue factor and podoplanin. Activated neutrophils release extracellular traps that activate coagulation and platelets. Venous stasis is common in patients with advanced cancer. Catheter placement and chemotherapy cause vascular endothelial damage.

to help physicians better manage CAT in cancer patients [8, 9]. These guidelines recommend use of low molecular weight heparin or direct oral anticoagulants for prevention of CAT, but unfortunately use of these drugs is not approved in Japan. This gap between Japan and other countries needs to be addressed.

We should also be aware of the risk of bleeding in cancer patients. Patients with advanced clinical cancer and acute leukemia often develop disseminated intravascular coagulation (DIC). Chemotherapy-induced thrombocytopenia is also associated with bleeding risk. Particular attention should be paid to prevention of CAT in these patients at high risk of bleeding. The ITAC clinical guidelines [8] describe the management of CAT in this special situation, which is presented in this special issue.

I hope that this special issue on cancer-associated thrombosis and bleeding will help you in your daily practice.

Declarations

Conflict of interest I have nothing to disclose.

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