Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

Mechanism and management of cancer-associated thrombosis

Mikio Mukai (MD, PhD)*, Toru Oka (MD, PhD)

Osaka Prefectural Hospital Organization, Osaka International Cancer Institute, Department of Medical Check up, Onco-Cardiology Unit, Osaka, Japan

ARTICLE INFO

Article history:
Received 23 February 2018
Accepted 27 February 2018
Available online xxx

Keywords:
Cancer
Venous thromboembolism
Atrial thromboembolism
Anti-angiogenic agents
Direct oral anticoagulants

ABSTRACT

Thromboembolism is considered to have a substantial impact on outcomes in patients with cancer. Although progress in cancer therapy and the advent of new anticancer agents such as molecular targeted drugs have improved the outcomes of patients with cancer, the incidence of cancer-therapy-related thromboembolism is increasing, and the management of this adverse reaction has become a major problem. Cancer is intimately related to thrombosis. Thrombus formation results from the complex interaction of various factors, such as tissue factors, coagulation abnormalities, activated platelet activation, activated adhesion activation, and endothelial cell dysfunction. Thrombosis has an impact on cancer proliferation and extension. The condition known as “cancer-related thrombosis” must therefore be managed differently from thrombosis in patients without cancer.

Contents

Introduction

The history of the relation between cancer and thrombosis dates back to 1823, the year in which Bouilland first reported that cancer is related to thrombosis [1]. In 1865, Trousseau reported a relation between potential cancer and migrating thrombophlebitis [2]. Thromboembolism is the second leading cause of death in patients with cancer who receive chemotherapy on an outpatient basis. Cancer therapy is therefore considered intimately related to thromboembolism, and thromboembolism is the most important cardiovascular complication in patients who receive cancer treatment [3]. Venous thromboembolism (VTE) is the most common type of thromboembolism occurring in patients during cancer treatment. Recent studies of patients with VTE have reported that the incidence of VTE is increasing year by year in patients with cancer. On the other hand, the advent of new molecular targeted drugs for cancer has led to increased risks of atrial thromboembolism (ATE) as well as VTE. These phenomena have suggested that the mechanisms leading to the development of thromboembolism in patients with cancer are diverse [4,5]. Therefore, thrombosis developing as a complication of

* Corresponding author at: Osaka Prefectural Hospital Organization, Osaka International Cancer Institute, Department of Medical Check up, Onco-Cardiology Unit, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan.
E-mail address: mukai-mi@mc.pref.osaka.jp (M. Mukai).

https://doi.org/10.1016/j.jjcc.2018.02.011
0914-5087/

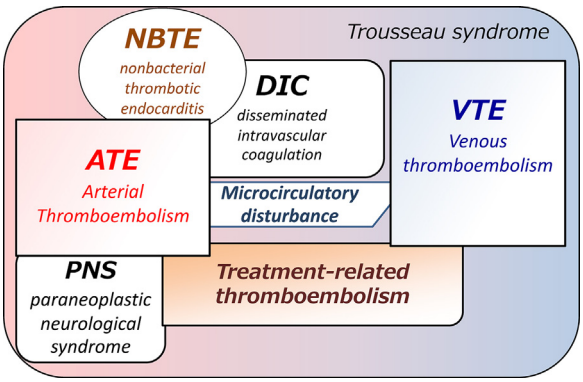

Fig. 1. Cancer-associated thrombosis. Thromboembolism that develops during cancer treatment is classified as arterial thromboembolism and venous thromboembolism, but multiple pathologies are considered depending on the onset mechanism. These thromboses are collectively referred to as cancer-associated thrombosis.

cancer is referred to as "cancer-associated thrombosis (CAT)" (Fig. 1). In this report, we review the characteristics and pathologic features of CAT.

CAT and its mechanism

The mechanisms of thrombosis occurring as a complication of cancer are shown in Fig. 2. Cancer tissue is in a state of coagulopathy, inflammation, and hypoxia, and various substances are produced by the induction of cancer proliferation genes, resulting in the formation of thrombi. The series of reactions involved in thrombus formation are related to the proliferation and metastasis of cancer [6]. Thrombosis in patients with cancer proceeds by a different mechanism from that in patients without cancer. Thrombosis developing in patients with cancer is treated as CAT [7]. Tissue factors (TFs) produced by cancer cells are considered the starting point of coagulation reactions that trigger CAT. TF activates factor VII, and a complex is formed between factor VII and TF. The TF complex promotes the activation of factor X, leading to the formation of factor Xa. On the other hand, some types of cancer cells produce cancer procoagulant (CP) and directly act on factor Xa. Factor Xa activated by these factors produces thrombin and simultaneously stimulates and amplifies the coagulation cascade. The amplified coagulation cascade further promotes platelet activation, leading to the formation of many thrombi on the vascular endothelium.

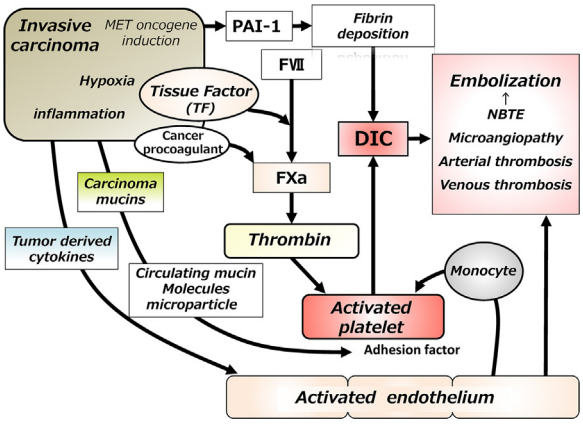

Fig. 2. Multiple mechanisms in cancer-associated thrombosis. There are multiple, overlapping, and interacting mechanisms that can explain the increased incidence of thrombosis in patients with malignancies. In cancer-associated thrombosis, hypercoagulability is probably the result of products arising from the tumor itself. CP, cancer procoagulant; DIC, disseminated intravascular coagulation; NBTE, nonbacterial thrombotic endocarditis; PAI-1, plasminogen activator inhibitor-1.

After microparticles including TF and adhesion factors are carried in the bloodstream, pathologic thrombi are formed on vascular endothelial cells that were damaged by cytokines produced by cancer cells. Plasminogen activator inhibitor (PAI)-1 secreted by cancer cells inhibits the fibrinolytic system, promoting the deposition of fibrin and leading to the formation of fibrin thrombi. Formed thrombin, activated platelets, fibrin, and abnormalities of coagulation and fibrinolysis can lead to the development of disseminated intravascular coagulation (DIC). In patients with cancer, pathologic thrombi are formed by complex coagulation mechanisms involving platelets and leukocytes (mainly monocytes) induced by the action of coagulation cascades and the activation of vascular endothelial cells. The mechanisms of these coagulation abnormalities and thrombosis may play important roles in the metastasis and proliferation of cancer cells as well as the presence of thromboembolism [8].

Venous thromboembolism

The common type of thromboembolism associated with the diagnosis and treatment of cancer is VTE. VTE is found in 10–20% of patients with cancer. The incidence of VTE in patients with cancer is estimated to be 4–7 times higher than that in patients without cancer [9,10] and has been increasing year by year. One of the reasons for this increase is that progress in lower extremity venous ultrasonography and contrast-enhanced computed tomography (CT) has enhanced the diagnosis of thromboembolism. Second, improved outcomes in patients with cancer have prolonged the duration of cancer therapy. Third, the development and increased use of new anticancer treatments, particularly molecular targeted drugs, have led to an increase in the incidence of treatment-related thromboembolism in patients with cancer [11]. The characteristics contributing to the pathogenesis of VTE in patients with cancer are shown according to Virchow's triad in Table 1. Venous stasis can be caused by factors such as prolonged bed rest (such as after surgery) and compression of blood vessels by tumors or ascites (particularly, in the pelvic cavity). Hypercoagulability can be caused by dehydration, malnutrition, transfusions, postoperative conditions, coagulation-promoting factors secreted by tumor cells, platelet activation, and chemotherapy. Vascular endothelial injury is likely to be caused by direct tumor invasion, the placement of venous catheters, injury by substances produced by tumors, chemotherapy, and radiotherapy [12].

Clinical signs and symptoms such as chest symptoms and leg edema have an important role in the diagnosis of VTE and are assessed according to the Wells score. Diagnostic imaging studies

Table 1
Virchow's triad in patients with cancer.

1. Venous stasis
• Prolonged bed rest/immobility (after surgery)
• Compression of blood vessels by tumor
2. Hypercoagulability
• Procoagulant effects
• Tumor cytokines
• Recent major surgery
• Active chemotherapy, hormonal therapy
• Current erythropoiesis-stimulating agents
• Current or recent antiangiogenic therapy
3. Endothelial injury
• Direct invasion by tumor
• Damaged or dysfunctional endothelium
• Tumor cytokine
• Presence of central venous catheters
• Chemotherapy drugs
• Radiation therapy (late phase complication)

Please cite this article in press as: Mukai M, Oka T. Mechanism and management of cancer-associated thrombosis. J Cardiol (2018), https://doi.org/10.1016/j.jjcc.2018.02.011