Thrombosis and Hemostatic Abnormalities in Hematological Malignancies

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Abstract

There is a paucity of data that pertain to thrombosis in patients with hematological malignancies. Recent studies showed that patients with lymphoma, multiple myeloma, and acute leukemia have an increased thrombotic risk, particularly at the time of diagnosis and during chemotherapy. We searched the PubMed database for articles on thromboembolic complications in patients with hematological malignancies published between 1996 and 2013. The incidence of thrombotic events is variable, and is influenced by the type and the stage of hematological malignancy, the antitumor therapy, and the use of central venous devices. The pathogenesis of thromboembolic disease in hematological malignancies is multifactorial. Tumor cell-derived procoagulant, fibrinolytic, or proteolytic factors, and inflammatory cytokines affect clotting activation, and chemotherapy and immunomodulatory drugs increase the thrombotic risk in patients with lymphoma, acute leukemia, and multiple myeloma. Infections might also contribute to the pathogenesis of the thromboembolic complications: endotoxins from gram-negative bacteria induce the release of tissue factor, tumor necrosis factor and interleukin-1b, and gram-positive organisms can release bacterial muco-polysaccharides that directly activate factor XII. In the setting of plasma cell dyscrasias, hyperviscosity, decreased fibrinolysis, procoagulant autoantibody production, inflammatory cytokines, acquired activated protein C resistance, and the prothrombotic effects of antimyeloma agents might be the cause of thromboembolic complications. Anti-coagulant therapy is very complicated because of high risk of hemorrhage. Therefore, an accurate estimate of a patient's thrombotic risk is essential to allow physicians to target thromboprophylaxis in high-risk patients.

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Introduction

The incidence of thromboembolic complications in solid cancer patients is about 5-fold greater than in the general population. Approximately 10% to 15% of patients with overt cancer will have a thrombotic complication during the course of the disease, but the rate of thrombosis in cancer varies greatly from 0.1% to 60% in relation to the tumor type, stage, and treatment (surgery, chemotherapy, radiotherapy, or hormonal treatments). Furthermore, venous thromboembolism (VTE) represents the second cause of morbidity and mortality in cancer patients.[1-4]

Recent studies have shown that the incidence of thrombosis might be as high (or even higher) in patients with malignant hematological disorders, but there is a paucity of data that pertain to patients with hematological malignancies.[5-10] Moreover, the patients included in the published case series often differ for the type and the stage of hematological malignancy, the antitumor therapy received, and the use of central venous devices (CVDs), thus making it difficult to draw any meaningful conclusions from the published data.[11-17] Clinically silent hemostatic abnormalities are found in most patients affected by hematological malignancies but only a limited number of patients show clinical manifestations including VTE, pulmonary embolism (PE), disseminated intravascular coagulopathy (DIC), and life-threatening thrombohemorrhagic syndrome, in which thrombosis and bleeding can occur concomitantly.[9] However, in hematological patients, the risk of thrombosis might be obscured by the significant morbidity and mortality due to other complications, such as bleeding and infection. The incidence of these complications depends on the type of hematological malignancy and the phase of treatment.[18] In addition, the widespread use of CVDs and the introduction of new immunomodulatory drugs (IMIDs), together with the use of erythropoietin and high doses of steroids have further increased the incidence of thrombotic complications. The pathogenesis of thromboembolic disease in hematological malignancies is complex

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and multifactorial, and can be due to the underlying disorder or related to therapy. Prothrombotic factors include hyperleukocytosis, increased tissue factor (TF) expression and activation in leukemic cells, and the prothrombotic effects of therapeutic agents and vascular access devices. In addition, comorbidities, including hereditary thrombophilia, infections, cytokine-induced endothelial cell activation, antiphospholipid syndrome, and acquired activated protein C resistance, are major contributory factors.[9,10] However, anticoagulant therapy is often complicated in hematological cancer patients, who are at very high hemorrhagic risk because of concomitant thrombocytopenia. Therefore, an accurate estimate of an individual patient's VTE risk, based on individual clinical risk factors and biomarkers, is essential to allow physicians to target thromboprophylaxis in high-risk patients. In this review article we will discuss the incidence, pathogenesis, risk factors, and the prophylaxis of thromboembolic complications and treatment of VTE in malignant hematological disease. Philadelphia-negative myeloproliferative neoplasms have not been included because thrombosis an intrinsic manifestation of these diseases.

Materials and Methods

The citations from PubMed between January 1996 and March 2013 were searched using the keywords "thrombotic events," "pulmonary embolism," and "hematological malignancies," "acute leukemia," "lymphoproliferative disease," and "multiple myeloma." Our search was limited to randomized controlled trials without language restriction. To ensure completeness of the search strategy, we independently searched the citations using databases from the Web of Science, EMBASE, and the Cochrane Library for all relevant randomized controlled trials. When there was a duplication of publications, we reviewed each article and included only the most recent or the most complete version of the trial for analysis.

Pathogenetic Mechanism of Thrombosis in Acute Leukemia

The Pathogenesis of Thromboembolic Disease in Acute Leukemias

The pathogenesis of thromboembolic disease in leukemia is complex and multifactorial. The major determinants are: (1) prothrombotic factors produced by leukemic cells, including TF, cancer procoagulant (CP), and inflammatory cytokine; (2) therapeutic agents used; (3) infectious complications; and (4) comorbid thrombophilia.[9]

Prothrombotic Factors Produced by Leukemic Cells

Prothrombotic factors produced by blasts cells, including TF, CP, and inflammatory cytokines, might induce the development of DIC and thrombin generation.

Cancer procoagulant is a cysteine protease derived from a broad spectrum of malignant and embryonic tissues that have vitamin K-dependent activity and directly activate factor X in the absence of factor VII.[19-21]

Increased levels of CP have been reported in various advanced cancers and acute promyelocytic leukemia (APL). The leukemic promyelocytes show the highest procoagulant activity and thrombin generation correlates with blast cell count in APL. The procoagulant state in APL is partially due to the TF-dependent procoagulant properties of circulating promyelocytic-derived microparticles (MPs).[22]

Leukocytosis is commonly observed in leukemia. Studies on the pathophysiology of leukostasis and tissue infiltration by leukemic blast cells have revealed that cytokines (tumor necrosis factor-alpha [TNF-alpha] and interleukin 1b [IL1b]) secreted by leukemic cells, together with direct contact between adhesion receptors expressed by blasts and endothelial cells, are responsible for endothelial activation, that leads to the activation of the clotting cascade and thrombotic complications.[23]

A summary of the pathophysiological mechanisms leading to thrombosis in cancer and specifically in hematological malignancies is represented in Figure 1.

Therapeutic Agents

L asparginase and steroids, typically used during induction treatment of acute lymphoblastic leukemia (ALL), have been shown to suppress natural anticoagulants, especially antithrombin and plasminogen, and cause increases in factor VIII and von Willebrand factor (vWF) complex.[24]

All-*trans*-retinoic acid (ATRA), used to treat APL, instead has been shown to decreases the expression of TF and CP, thus reducing blast cell procoagulant activity, fibrinolytic and proteolytic activities, and the secretion of inflammatory and angiogenetic cytokines.[25,26] However, ATRA also increases the production of cytokines affecting endothelial status, and might be involved in activating the prothrombotic and proadhesive functions of the endothelium and some studies have suggested that ATRA-induced modifications in the balance between procoagulant and fibrinolytic properties of leukemic promyelocytes might favor the development of prothrombotic events, especially during ATRA syndrome and in patients with hyperleukocytosis.[27]

Moreover, retinoic acid isomers (either ATRA or 13-*cis*-retinoic acid) might also contribute to an increased thrombotic risk by altering serum triglyceride metabolism, which leads to the hypertriglyceridemia often observed in patients treated with either retinoids or rexinoids. This appears to be secondary to a reduced capacity to clear infused lipids, suggesting reduced tissue lipolytic activity.[28]

Based on these experimental data we conclude that ATRA-induced hypertriglyceridemia, in addition to ATRA-induced hypercoagulability, might contribute to venous and arterial thromboembolic events in patients with hematological malignancies and in fact thromboembolic events have been reported during ATRA therapy including myocardial infarction, cerebral thrombosis, and VTE.[9]

Infectious Complications

Endotoxins from gram-negative bacteria induce the release of TF, TNF-alpha, and IL1b, and gram-positive organisms can release bacterial mucopolysaccharides that directly activate FXII.[29]

Comorbid Thrombophilia

Age, hospitalization-related immobility, and especially the presence of a CVD are additional important factors that contribute to the development of thrombosis. The pathogenesis of CVD-related thrombosis is multifactorial, and the risk factors include CVD