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Arterial thrombosis and cancer

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ABSTRACT

Cancer-associated arterial thrombotic events (ATEs) are increasingly recognized in specific malignancies and in association with the expanding armamentarium of novel chemotherapeutic agents. The improved cancer survival led to cardiovascular complications becoming clinically relevant many years after cancer diagnosis. The pathobiology of ATEs in cancer is complex and the individual patient risk for an ATE entails a multifactorial interaction between the traditional cardiovascular risk factors and comorbidities, the specific malignancy and selected therapy. Treatment with several specific chemotherapeutic agents, immunomodulatory drugs, vascular endothelial growth factor pathway inhibitors, tyrosine kinase inhibitors, and radiotherapy, impart increased risk for ATEs that result from specific therapy-related mechanisms, often involving endothelial injury. Cancer cell-specific prothrombotic properties are important players in the pathogenesis of cancer-associated hypercoagulability. There are distinct biological and molecular processes preferentially activated in specific cancer cells which can trigger ATEs, including platelet activation, increased expression of procoagulants and suppression of fibrinolytic activity. ATEs portend adverse prognosis in cancer patients. Prevention and treatment of cancer-associated ATEs may be improved by greater awareness and careful monitoring for vascular toxicity, aggressive effort to optimize conventional cardiovascular risk factors, and use of antiplatelet and antithrombotic agents in selected patients. These issues are targets for future studies aimed to reduce ATEs in patients with cancer.

1. Introduction

Cancer is associated with an increased incidence of thrombosis. There are considerably more data on venous thromboembolism (VTE) than arterial thrombosis in cancer. Nevertheless, cancer-associated arterial thrombotic events (ATEs) are increasingly recognized in specific malignancies and in association with cancer therapies.

The pathogenesis of arterial thrombotic events in cancer is complex and the individual patient risk for an ATE entails a multifactorial interaction between the individual cardiovascular risk and comorbidities [1], the specific neoplasm and selected therapy (Fig. 1).

Risk factors for arterial and venous thromboses partially overlap. At the epidemiological level, an association exists between VTEs, ATEs (myocardial infarction and stroke) and atherosclerosis [2–4] that is attributed to shared risk factors. Furthermore, a pathogenic link between the venous and arterial thrombotic events is also suggested by recent evidence of reduced risk for ATEs with rivaroxaban added to aspirin [5]. In cancer patients this association is striking, as the cancer-associated hypercoagulability and certain chemotherapeutic regimens increase the risk of both VTEs and ATEs.

2. Pathobiology of acute arterial thrombotic events

Most atherosclerotic plaques remain asymptomatic, some become obstructive (causing stable angina) but a few become thrombosis-prone (vulnerable) leading to intraluminal thrombosis and acute events, such as myocardial infarction and stroke. Vulnerable plaques are frequently angiographically mild, and characterized by lipid-rich atheroma covered by thin fibrous layer [6]. Rupture of the fibrous cap exposes the procoagulant material within the plaque's core to platelets and coagulation proteins in the plasma, promoting thrombosis [7]. Thus, fundamental mechanism in the development of potentially life-threatening ATEs is thrombosis arising at sites of plaque disruption where activation of thrombosis progresses to persistent intraluminal thrombosis [8]. Not all disruptions of atherothrombotic plaques result in clinically apparent or symptomatic events. The systemic thrombogenicity and fibrinolytic potential at the time of plaque disruption may determine the degree of thrombus formation and, hence, the likelihood of clinical ATEs [9].

Cancer is characterized by a variety of individual alterations in platelet function [10–12] as well as in the coagulation and fibrinolytic systems [13,14] that combine to produce a prothrombotic state (Fig. 1).

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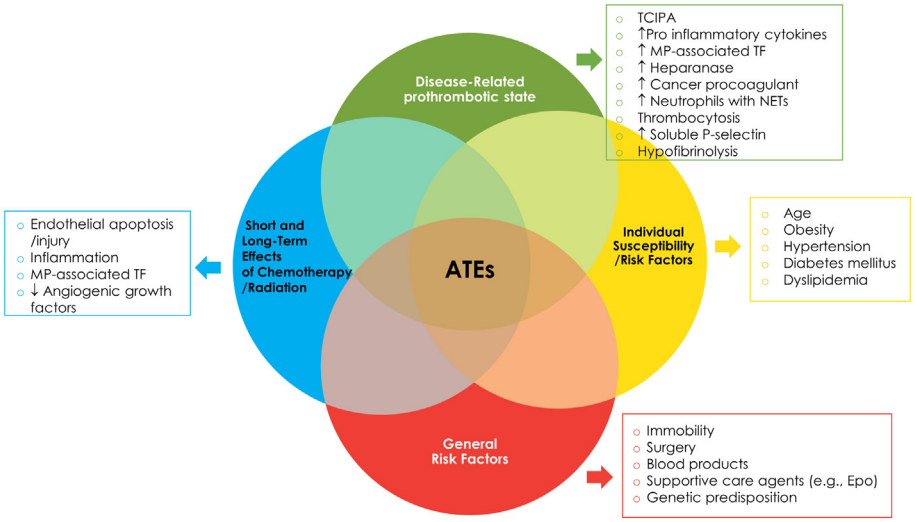

Fig. 1. The individual risk for arterial thrombotic events in cancer patients is determined by a complex interaction between multiple factors including baseline cardiovascular risk factors, cancer type and stage, the chemotherapeutic regimen and other general contributing factors for thrombosis.
MP = microparticles; NETs = neutrophil extracellular traps; TCIPA = tumor cell-induced platelet aggregation; TF Tissue factor.

The complex relationship between cancer and platelets is bidirectional, i.e., platelets influene tumor behavior and vice versa [15]. There is also growing evidence that platelets have a role in promoting the hypercoagulable state of malignancy [10–12]. Tumor cells have the ability in vitro to induce platelet activation and aggregation via several molecular pathways including the thrombin, ADP, thromboxane A_2, metalloproteinases and tissue factor (TF) pathways [11,12], collectively called tumor cell-induced platelet aggregation (TCIPA). In addition, cancer patient may have increased levels of markers of platelet activation, including soluble CD40 ligand, soluble P-selectin, and platelet factor 4 [10–12].

Endothelial *injury*, which results in endothelial *dysfunction*, has a central pathogenic role in the initiation and progression of atherosclerosis [16]. Several antineoplastic agents (e.g., vascular endothelial growth factor [VEGF] signaling pathway inhibitors, cisplatin) can cause direct endothelial damage, ultimately contributing to the progression of the atherosclerotic process [17] (Table 1).

3. Cancer therapy and arterial thrombotic events

There is a considerable overlap in risk factors and shared biology for ATEs and cancer (e.g., obesity, diabetes mellitus, smoking, chronic inflammation) [1]. Therefore, many patients diagnosed with cancer have increased baseline risk for ATEs. The risk of ATE increases in cancer patients receiving chemotherapy [18,19], and is highest soon after diagnosis, when treatment is administered for active cancer [20]. Active treatment with several specific chemotherapeutic agents and radiotherapy (RT), imparts a significant risk for thrombotic events, including ATEs that result from specific therapy-related mechanisms (Table 1) and a complex interaction with the underlying disease. Endothelial damage is a common mechanism for cytotoxic agents-associated ATEs [17]. In addition, late effects of chemotherapeutic agents and RT can increase the risk for ATEs years after the disease is no longer active.

3.1. Immunomodulatory drugs and proteasome inhibitors

Patients with multiple myeloma have increased mortality secondary to both arterial and venous thrombosis [21]. Immunomodulatory agents are known to increase the risk of thrombotic events, particularly when combined with high-dose steroids, doxorubicin or the concomitant use of erythropoietin [22,23]. Most thrombotic events described in patients receiving treatment with immunomodulatory agents have been venous, but ATEs (myocardial infarction and stroke) have also been reported with lenalidomide and pomalidomide. Data derived from two multicenter, randomized, double-blind, placebo-controlled, trials of lenalidomide plus dexamethasone versus dexamethasone alone in 704 patients with refractory or relapsed multiple myeloma, have shown that the incidence of myocardial infarction and cerebrovascular events is 1.98% and 3.4%, respectively, in patients treated with lenalidomide and dexamethasone compared with 0.57% and 1.7%, respectively, in patients treated with dexamethasone alone. Adding carfilzomib (a proteasome inhibitor) to lenalidomide and dexamethasone further increases the risk for cardiovascular toxic events, including ischemic heart disease (5.9% vs. 4.6%) [24]. By contrast, the proteasome inhibitor bortezomib, does not increase the risk of ATEs [25]. A thromboprotective effect of bortezomib has been suggested, mediated by increased expression of the transcription factor Kruppel-like factor 2 (KLF2) [26].

The International Myeloma Working Group recommends that during thalidomide or lenalidomide treatment, aspirin is indicated in low-risk patients (with one or no risk factors) and prophylactic low molecular weight heparin or dose-adjusted warfarin for 4–6 months followed by aspirin in high-risk patients (with 2 or more risk factors) [27].

Table 1
Mechanisms of therapy-related arterial thrombotic events in cancer patients.

Agent	Putative mechanism of arterial thrombosis
VEGF signaling pathway inhibitors	Endothelial dysfunction, increase the expression of proinflammatory cytokines [32]
Fluoropyrimidines	Vasospasm, endothelial injury [44]
Tyrosine kinase inhibitors	Endothelial dysfunction, increase the expression of proinflammatory cytokines [88]
Cisplatin	Endothelial injury [61]
Proteasome inhibitors	Increased levels of coagulation factors and pro-inflammatory cytokines, increased microparticle-associated tissue factor activity, hypofibrinolysis [25,89]
Radiation therapy	Endothelial dysfunction, inflammation, oxidative stress, alterations of coagulation and platelet activity, DNA damage, vascular senescence and apoptosis [90]