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Review

Arterial Thrombosis in Cancer: Spotlight on the Neglected Vessels

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Abstract. *Cancer patients are at risk for both venous and arterial thrombotic events. Accumulating evidence suggests a link between cancer and arterial thrombosis events. The pathophysiology of arterial thrombosis in cancer is complex and multifactorial. The risk of arterial thrombosis in cancer patients relies on individual risk factors, on cancer-related hypercoagulability, on anticancer drugs and radiotherapy often via a common underlying mechanism of endothelial dysfunction. This review describes the mechanisms involved in the development of arterial thrombotic events and their clinical manifestations. Furthermore, it provides an overview on therapeutic agents associated with arterial thrombosis.*

Improvements in anti-cancer global strategy resulted into a better outcome of a large percentage of cancer patients many of which experience definitive cure or long-term survival. As a consequence, toxicities claim attention and physicians should also focus on the long-term management of drug-induced side effects mainly related to the cardiovascular system. Cancer is a risk factor for both venous (VTEs) and arterial thrombotic (ATEs) events. The risk of VTEs in cancer patients is clearly defined with a roughly 7-fold increase compared to the general population (1).

Arterial thrombotic events are increasingly reported in cancer patients both during active treatment and follow-up with various clinical manifestations. The appearance of ATEs is associated with a worse prognosis and a 3-fold increase in overall mortality risk and a probability of recurrent thromboembolism of 37% at six months (2, 3). According to National Cancer Institute's Common Toxicity Criteria, arterial thromboembolism adverse events in cancer patients are related to myocardial ischemia or infarction, cerebral infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral or visceral arterial thrombotic events so highlighting the wide spectrum of possible clinical presentations (4).

Tumor cells directly and indirectly induce a state of hypercoagulability through distinct molecular pathways. Platelet activation, increased synthesis of procoagulant factors and reduction of fibrinolytic activity are all triggers for ATEs. Moreover, local and systemic inflammatory stimuli can turn the endothelium into a pro-thrombotic surface. All these mechanisms could be amplified by anticancer drugs and radiotherapy.

Epidemiology

Epidemiology of arterial thrombosis has received more attention in recent years. Navi *et al*., using the Surveillance, Epidemiology, and End Results (SEER) database from 2002 to 2011, have analyzed the incidence of ATEs (as arterial thromboembolic events, myocardial infarction or stroke) in a large population of 279,719 of newly diagnosed cancer patients (2). Compared to an age and sex matched control group they found a cumulative incidence of arterial thromboembolism of 4.7% in all cancer patients *vs*. 2.2% at 6 months. The risk is higher in some types of tumours such as lung, gastric, and pancreatic. Advance stage was associated with increased ATEs risk, with stage IV patients having a >10-fold increase in ATE in the first month after diagnosis of cancer (2).

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A cohort study performed in Taiwan on 52,089 patients with lung cancer and 104,178 matched controls has shown an 1.5 increase in the risk of ischemic stroke in cancer patients (5). This higher risk showed a time trend with a decrease after the first year in men and after the second year in women.

A personal history of cancer-related ATE is associated with a subsequent higher risk of recurrence of thrombosis. Cancer patients with acute ischemic stroke showed a high rate of recurrent ATEs of 21, 31, and 37% at 1, 3, and 6 months, respectively, with adenocarcinoma having the highest rates of recurrence (3). Grilz *et al*., in an update of CATS study, have reported an overall incidence of arterial thromboembolism of 2,6% at two years of observation more frequently reported in lung and kidney cancer patients (6). Interestingly, classic cardiovascular risk factors such as age, male sex, and smoking were found to be independent risk factors for ATE in the CATS cohort.

Pathogenesis

The pathogenesis of ATEs in cancer is multifactorial and includes individual cardiovascular risk, comorbidities, cancer site and stage and anticancer drugs or radiotherapy.

Cancer cells can express procoagulant factors. Tissue factor (TF) is the receptor for factor (F) VII and site of activation of FVII and FVIIA. TF results in activation of coagulation cascade when it comes into contact with activated FVIIa resulting in local generation of thrombin, the most potent platelet activator (7). An alternative coagulation pathway is *via* cysteine protein (CP) that activates FX in the absence of FVII. Activation of procoagulant factors can occur during apoptosis of tumor cells induced by chemotherapeutic agents, hypoxia, radiation or haematological growth factors (7, 8). Moreover, a reduction in fibrinolysis is involved in tumor growth and metastasis (1). Cancer can activate the coagulation cascade in several ways including the induction of platelets, monocytes and endothelial cells to express a procoagulant phenotype. A reduction in molecules such as antithrombin, proteins C and S, and tissue plasminogen activator can contribute to the development of arterial thrombosis in cancer (7, 8).

Tumor cells can produce ligands including thrombin, ADP, thromboxane A2, metalloproteinases (MMPs) and TF. In response, the stimulation of platelet surface receptors (*e.g*., PAR-1 and PAR-4 receptors, P2Y12 receptor, and thromboxane receptor) can mediate platelet activation (8, 9). Sound evidence indicates increased levels of markers of platelet activation in cancer, including soluble P-selectin, soluble CD40 ligand, platelet factor 4. Cancer leads neutrophils to release decondensed chromatin with formation of extracellular traps so promoting inflammation and thrombosis. Platelets play a pivotal role in tumor progression and metastasis by promoting a hypercoagulability state and, as a consequence, thrombocytosis is a maker of cancer associated thrombosis (9, 10).

Clinical Presentation

Arterial thrombosis may occur in any vessel including limb, myocardial and brain. Clinical presentation of arterial thromboembolism can be acute or subacute, leading to ischemia or infarction with symptoms related to the affected organ. As previously stated, the risk of arterial thromboembolism depends on older age, common cardiovascular risk factors and both cancer and treatment-related factors (11). Stroke or myocardial infarction may be the first manifestation of malignant tumours when their cause is not clear (12). The presence of a hypercoagulable state (high levels of D-dimer, diffuse intravascular coagulation) could suggest the need of a screening for undiagnosed cancer. The clinical presentation of ischemic stroke in cancer patients does not grossly differ from that of the general population but sometimes some differences could be identified. A study reported that the percentage of cryptogenic strokes is higher (30 *vs*. 50%) in cancer patients with multiple localizations and consequent encephalopathy (3, 13). A hypothesis suggests thrombotic endocarditis as possible cause of stroke in cancer patients. This phenomenon could be confirmed by high levels of D-dimer, while it is difficult to be diagnosed *in vivo* and is more frequently found at autopsy (3). Another possible mechanism for stroke in cancer is paradoxical embolism taking into consideration that about 20% of cancer patients develop venous thromboembolism or septic embolism (related to infective endocarditis due to the presence of catheters or invasive procedures). Brain tumors remain the main etiology for stroke (14, 15).

Cancer patients have a risk of recurrent ischemic stroke approximately 3-fold higher than non-cancer patients both during active cancer (16) and later due to radiotherapy damage as reported in the Childhood Cancer Survivor Study (17). A recent metanalysis that included 9711 renal cell carcinoma patients from 19 randomized controlled trials (RCT) confirmed an overall incidence of ATE of 1.5%. The most common events for ATEs were cardiac ischemia/infarction (67.4%), CNS ischemia (7.9%) and cerebrovascular accident (6.7%). The highest ATE incidences were noted for cediranib (3.2%) and pazopanib (2.4%), and recurrence rates were confirmed to be significantly elevated for pazopanib [4.6 (95%CI=1.1-18.7)] and sorafenib [2.3 (95%CI=1.2-4.4)] only (18).

Peripheral arterial thrombosis is mainly described with the new-generation BCR-ABL inhibitors such as nilitinib, dasatinib and more frequently with ponatinib. Treatment-related events may be rapidly progressive and also continue after discontinuation (19).

Drug-related Arterial Thrombosis

Angiogenesis inhibitors. Angiogenesis plays an important role in cancer growth, invasion, and metastasis. Inhibition of vascular endothelial growth factor (VEGF) signaling pathway, one of the key paths in cancer neo-angiogenesis control, could lead to endothelial cell damage resulting in vascular toxicity. In clinical practice several angiogenesis inhibitors are utilized for the management of solid and hematologic malignancies.

Anti-VEGF antibodies. Bevacizumab is a recombinant, humanized monoclonal antibody directed against VEGF used in the treatment of many cancer types. ATEs are described with a relatively high frequency but rates vary among trials. In an analysis of pooled data from five RCTs including 1745 patients with metastatic colorectal, breast, or non-small-cell lung carcinoma, the addition of bevacizumab to chemotherapy was associated with an increased risk of ATEs (overall incidence 3.8% with bevacizumab *vs*. 1.7% in the chemotherapy group) (20). In a meta-analysis of 20 RCTs including 12.617 patients with various advanced solid tumors, bevacizumab treatment was associated with an increased risk of all ATEs of 3.3%. The risk of myocardial infarction was higher with bevacizumab, while no difference was described regarding to ischemic stroke (21). A subsequent meta-analysis of 22 prospective trials enrolling more than 20,000 patients found a higher risk of cardiac and cerebral ischemia in patients receiving bevacizumab compared to chemotherapy. The risk seemed to be directly proportional to the dose of bevacizumab with patients receiving higher doses being at higher risk (22). These findings have not been fully confirmed in a large observational study reporting that the relative risk of ATEs with bevacizumab-based therapy compared with controls was 1.46% and on subgroup analysis the risk was independent from cancer site, bevacizumab dose or disease stage (23).

It has been proposed that bevacizumab-related endothelial damage with decrease in nitric oxide and PGI-2 synthesis could lead to activation of platelet and coagulation factors resulting in arterial thrombosis (24).

A similar rate of arterial adverse events was reported for aflibercept, a recombinant fusion protein containing VEGF-binding portions fused to the Fc portion of human immunoglobulin (Ig)G1 used in the treatment of advanced refractory colorectal cancer. All grade and serious arterial thromboembolic adverse events that were reported with a relatively low incidence in VELOUR trial (2.6 and 1.8% respectively), have been recently confirmed by real word data reporting an incidence of arterial or venous embolic events of 6% (25, 26).

Ramucirumab, a novel fully human IgG1 monoclonal antibody that selectively targets VEGFR-2, was not associated with increased risk of ATE (27).

Immunomodulatory agents. The risk of tromboembolism in patients receiving lenalidomide and pomalidomide especially when administrated with dexametazone or other chemotherapy is high with a global incidence of 8.5% (28). The mechanism of vascular toxicity is not completely understood. Endothelial damage with reduced production of nitric oxide can led to ischemia/coronary disease and the association with steroids can enhance endothelial stress resulting in platelet activation and thrombosis (28).

Tyrosine kinase inhibitors. Small-molecule inhibitors against receptor tyrosine kinases in cancer cells has dramatically improved survival in several cancer types. In general, the toxicity profile of these drugs differs from those of classic chemotherapy but arterial thrombotic events have been reported. In a meta-analysis by Choueri *et al*. including 10,255 patients with advanced renal cell carcinoma and other malignancies receiving sorafenib or sunitinib, authors reported an incidence of arterial thrombosis of 1.4% compared with the control group, with no difference between renal and non-renal cancer or between the two drugs (29). A subsequent meta-analysis of 9,711 patients from 19 RCTs showed an overall incidence of ATEs of 1.5% (18). The subgroup analyses did not show a significant difference in terms of risk of ATE depending on tumor types, VEGFR-tyrosine kinase inhibitors (TKIs), treatment regimens, phase of trials and sample size. Additionally, the most common events for ATEs were cardiac ischemia/infarction (67.4%), CNS ischemia (7.9%) and cerebrovascular accident (6.7%). Few data are available for others VEGF-TKIs; a comparative meta-analysis of random trials showed no increase in the risk of thrombosis (RR 0.85) for axitinib, cediranib and regorafenib compared to standard treatment (30). A recent systematic meta-analysis focused cardiovascular issues of regorafenib treatment; while hypertension and bleeding were significantly more frequent, arterial thrombosis and heart failure were not (31).

Pazopanib may be responsible for apoptosis of endothelial cells, which promotes coagulation, thus leading to thromboembolic and ischemic events in treated patients. Moreover, its inhibition of VEGF signaling may also increase blood viscosity through overproduction of erythropoietin, exacerbating risk for thrombosis, but ATEs (miocardial infarction/ischemia, cerebrovascular events) are uncommon with pazopanib (<2%) in clinical practice (32). To date, no specific data are available about ATEs risk with other VEFG inhibitors as cabozantinib, vandetanib or nintebanib.

BCR-ABL1 kinase inhibitors. Imatinib dramatically changed prognosis of chronic myeloid leukemia (CML) and subsequently gastro-intestinal stromal tumors patients and is considered as a milestone in target therapy development.

The new-generation BCR-ABL TKIs, designed to overcome imatinib resistance, including nilotinib, dasatinib, bosutinib, and ponatinib are associated with a higher risk of arterial events compared with the standard imatinib (33). Random trials have reported a higher incidence of cardiovascular events with nilotinib treatment compared to imatinib including peripheral arterial occlusive disease and other vascular events (*i.e.* myocardial infarction and pulmonary embolism). Similar to nilotinib, dasatinib has been associated with a greater rate of ischemic events compared with imatinib. Ponatibib, initially withdrawn by the FDA for high rate of ATEs, can result in peripheral arterial occlusive disease that may be rapidly progressive and these events can continue also after discontinuation of treatment. It may also cause cerebral ischemia and myocardial infarction (19). In patients receiving bosutinib at a lower dose (400 mg), ATEs events can occur less frequently compared with other BCR/ABL1 TKIs, but are still more common than with imatinib. Thrombotic events are more frequent in presence of cardiovascular risk factors but concur also without them. Possible mechanisms of such toxicity have not been clearly established but evidence supports inhibition of ABL kinase with endothelium injury (34).

Antimetabolites. 5-Fluorouracil (5-FU), a pyrimidine analogue, and capecitabine are cornerstones of treatment of gastrointestinal and breast cancers. Ischemic events may occur during infusion or within 2-3 days from the beginning of therapy presenting as angina, acute myocardial infarction, heart failure and cardiogenic shock.

The incidence of ischemia is related to drug dose with higher risk associated to repeated infusions and to administration route. In fact, it is higher during continuous i.v. infusion compared to bolus administration or oral capecitabine. Electrocardiographic changes with S-T depression and T wave inversion are landmarks of acute ATEs and drug re-challenge is associated with higher risk of cardiac complications (35). The underlying mechanism remains unknown but coronary vasospasm has been reported is several cases; coronary angiography performed immediately after acute event frequently showed no culprit lesions. In that cases, drug infusion could interfere with pathways that mediate vascular smooth muscle tone (36). Another possible mechanism is damage of the arterial endothelium followed by thrombosis (37).

Alkylating agents. Coronary thrombosis is the basis of myocardial infarction associated with platinum compounds. Acute ATEs may develop during or even after cisplatin-based chemotherapy combinations (38). An increased risk of atherosclerotic disease has been described after 10-20 years in testicular cancer survivors, with a percentage ranging from 6% to 10% and even higher when treatment was associated with radiotherapy (39). A possible explanation relies on the fact that cisplatin blood levels may remain elevated for many years after therapy discontinuation leading to a long-lasting risk (40). Ischemic stroke is another possible complication of cisplatin-based chemotherapy in young patients probably due to a direct endothelial damage leading to platelet and coagulation cascade activation (41). Together with cisplatin, cyclophosphamide (mainly at high dose) is associated with acute myocardial infarction and stroke. Probably, the two drugs share endothelial damage and platelet adhesion as triggers for toxicity (42).

Radiotherapy. Mediastinum irradiation is associated with several cardiovascular complications. Coronaropathy could be reported long time after exposure, typically 10 to 15 years, mainly involving coronary arteries and distal vessel (43). Cardiovascular toxicity of radiotherapy is dose related. Survivors of Hodgkin lymphoma have 2.7-fold higher risk for coronary heart disease compared to general population (44). Interestingly, when mediastinum is included in treatment field, aorta or great vessels could be targets of late toxicity (45).

Radiotherapy of head and neck tumors could be associated with carotid arteries atherosclerosis with significant internal and common carotid stenosis resulting in transient ischemic attack or ischemic stroke while radiation treatment of brain tumors (mainly involving the circle of Willis) could lead to a later higher risk of stroke in survivors (46).

Independently of the site of treatment, radiotherapy causes early inflammation of the whole arterial wall, followed by vascular fibrosis that can occur in any layer of the vessel wall usually in medium and large size vessels (47). Moreover, irradiation is involved in atherosclerotic plaque formation and accelerates atherosclerosis process (48).

Aromatase inhibitors. Aromatase inhibitors (AIs) are used as adjuvant therapy in hormone receptor-positive post-menopausal early breast cancer patients. A meta-analysis that analyzed switch strategy (tamoxifen followed by AIs) *vs*. upfront AIs treatment reported a small increase in cardiovascular adverse events with upfront AIs (4.2% *vs*. 3.4%) (49). Combined analysis of randomized control trials of AIs found a 19% increase risk of ischemic heart disease compared to tamoxifen. It should be noted that, in the adjuvant setting, tamoxifen was associated with a 33% decreased risk compared with placebo or no-treatment. Therefore, the increase in cardiovascular risk observed with AIs could be explained, at least in part, by the lack of the protective effect of tamoxifen (50).

Conclusion

Arterial thrombotic events represent serious and potentially life-threatening adverse events of a variety of anti-cancer

treatments. Their knowledge and management is of primary importance for both clinical cardiologists and oncologists involved in the care of cancer patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception: MLC, IP; Design: MLC, IP, IB, CL; Literature review and processing: MLC, IP, IB, CL; Writing: MLC, IP, CL; Critical review: MLC, IB, CL; Final approval: MLC, IP, IB, CL.

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