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Arterial Thrombosis in Patients with Cancer

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Abstract

Purpose of review—Cancer is a common cause of morbidity and mortality in the USA. While the association between venous thrombosis and malignancy is well established, arterial thrombosis has more recently been recognized as a serious complication of cancer and certain chemotherapeutic agents. This review aims to summarize the most recent literature regarding the incidence and risk factors for cancer-related arterial thrombosis, understand the pathophysiologic mechanisms of thrombosis, and highlight the specific diagnostic and treatment considerations relevant to cancer patients.

Recent findings—Based on a recent study looking at the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of arterial thromboembolic events (ATEs) in patients with cancer at 6 months is 4.7%; the presence of an ATE is predictive of worse outcomes. Certain drugs such as platinum-based agents, vascular endothelial growth factor inhibitors, tyrosine kinase inhibitors, and taxanes have been associated with high rates of ATEs. Increased platelet reactivity appears crucial to development of arterial thrombosis in cancer patients.

Summary—Cancer patients have an increased risk of arterial thrombosis that is likely due to both a cancer-associated procoagulant state as well as the adverse effects of certain chemotherapeutic agents. Treatment of arterial thromboembolism in cancer patients typically requires a multidisciplinary approach in part due to high rates of thrombocytopenia and stent thrombosis in the setting of percutaneous interventions. More studies are needed to investigate optimal prophylaxis, surveillance strategies, and treatments of cancer-related arterial thromboembolic disease.

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Conflict of Interest

Mirela Tuzovic, Cezar Iliescu, Kostas Marmagkiolis, Boback Ziaeian, and Eric H. Yang each declare no potential conflicts of interest. Joerg Herrmann was a participant in the 2014 Ponatinib in CML Cardio-Oncology Advisory Board meeting organized by ARIAD Pharmaceuticals and the 2015 Advisory Board meeting of the Institute for Cardio-Oncology sponsored by Bristol-Myers Squibb.

Keywords

Arterial thrombosis; Cancer; Chemotherapy

Introduction

Cancer is a leading cause of morbidity and mortality in the USA [1] afflicting approximately 40% of people at some point in their lifetime [2]. With newer and more effective treatments, many patients live for years or even decades after an initial cancer diagnosis. In fact, there are an estimated 15.5 million children and adult cancer survivors in the USA as of 2016 [3], and this number is expected to increase to 20.3 million by year 2026 [3].

Patients with cancer experience a high burden of thromboembolic disease [4]. Traditionally, the main consideration has been given to venous thrombotic events in this population; however, in 2011, Blann et al. [5] outlined that approximately 25% of all PubMed citations on thrombosis are on arterial thrombosis. In one prospective study of cancer patients receiving outpatient chemotherapy, arterial thrombosis accounted for 5.6% of deaths [4]. Here, we review the incidence and risk factors for cancer-related arterial thrombosis, the pathophysiologic mechanisms of thrombosis, and the specific diagnostic and treatment considerations relevant to cancer patients.

Epidemiology

Incidence of arterial thrombosis in cancer patients

Prior studies of hospitalized cancer patients have reported an incidence of arterial thrombosis of around 1.5–5.2% in this population [6, 7]. More recently, Navi et al. analyzed the Surveillance, Epidemiology, and End Results (SEER) database in order to characterize the incidence of ATE (arterial thromboembolic events, myocardial infarction or stroke) in cancer patients across the USA (Fig. 1) [8••]. The study included 279,719 pairs of patients with cancer and matched controls with a new diagnosis of cancer identified between 2002 and 2011. The cancer types included breast, lung, prostate, colorectal, bladder, pancreatic, gastric, and non-Hodgkin lymphoma. The incidence of ATE at 6 months was 4.7% in all cancer patients compared to 2.2% in the matched control cohort. Patients with lung, gastric, or pancreatic cancers had the highest rates of ATE (8.3, 6.5, and 5.9%, respectively). Ischemic stroke was less common in cancer patients than myocardial infarction (2.0% at 6 month follow-up versus 3.0% respectively). One-year after diagnosis, the risk for ATE was significantly attenuated in most cancer types. Advanced stage of cancer was associated with a significant increase in ATE (stage 0 2.3% incidence at 6 months compared to 7.7% for stage 4). ATE was associated with increased mortality even after matching for all factors and the stage of the cancer (hazard ratio 3.1, CI 3.0–3.1) [8••]. The 30-day cumulative incidence of death after ATE was 17.6 versus 11.6% in patients with cancer and controls, respectively [8••]. In the National Heart, Lung, and Blood Institute Dynamic Registry, a history of cancer was a significant predictor of 1-year death and myocardial infarction (MI) in patients who presented with an acute MI requiring percutaneous coronary intervention (PCI) [9]. A retrospective analysis of 261 patients with a history of cancer in the Mayo Clinic PCI

Registry of patients who underwent PCI for an ST segment elevation MI were found to have a three times higher risk of acute in-hospital and long-term non-cardiac mortality risk, but no increased acute or long-term cardiac mortality risk with evidence-based cardiac treatment and care [10].

The risk of recurrent ATE is not well described. One study evaluated cancer patients with acute ischemic stroke and showed that the rate of recurrent ATE in that population is 21, 31, and 37% at 1, 3, and 6 months, respectively. Among different cancer histologies, adenocarcinoma had the highest rates of recurrence (hazard ratio 1.65, CI 1.02–2.68) [11].

Malignancy appears to markedly increase the risk of in-stent thrombosis (IST) after percutaneous intervention. IST incidence in patients with known malignancies and bare metal stent(BMS) was reported at 5.56% ($p < 0.000001$, odds ratio 7.10, 95% confidence interval 2.70 to 17.61), with a median time to IST of 7 days. The majority of the patient were on dual anti-platelet therapy (DAPT, 83.3%) when the IST occurred [12].

Chemotherapy-related arterial thrombosis

Many chemotherapeutic agents are prothrombotic, and up until recently, the association between chemotherapy and arterial thrombosis was largely documented in case reports. Although it is difficult to precisely define the relative prothrombotic effects of the chemotherapy compared to the hypercoagulable state of malignancy, many chemotherapeutic agents have been associated with a high burden of ATE. The most common arterial thrombotic events include myocardial infarction (MI), cerebrovascular event (CVA), and peripheral artery disease (PAD). Platinum-based agents [13–15], vascular endothelial growth factor (VEGF) inhibitors [16–20], VEGF tyrosine kinase receptor inhibitors (TKI) [21–25], and Bcr-Abl TKI [26] have all been associated with increased rates of ATE. The reported incidence of ATE for different medications is shown in Table 1. Cisplatin (platinum-based agent) and ponatinib (Bcr-Abl TKI) have strikingly high rates of ATE (up to 8.3% [13] for cisplatin and 20% [26] for ponatinib). Of note, in 2013, the FDA requested a voluntary suspension of Ponatinib marketing until safety measures were implemented due to extremely high rates of vascular events during the post-marketing analysis. Patients with multiple myeloma who are treated with lenalidomide and dexamethasone also have a high rate of arterial thromboembolic events (MI 1.98% and CVA 3.4%) [55]. Medications such as bevacizumab (VEGF inhibitor), sorafenib/sunitinib/pazopanib (VEGF TKI), and tamoxifen (selective estrogen-receptor modulator) have more modest rates.

Cisplatin [14, 27, 28], nilotinib [22], ponatinib [26, 34], 5-FU [35, 37–42], and capecitabine [35–37] all have high incidence of coronary artery thrombotic events. However, there is some variation in the definition of cardiac events across studies and inclusion of non-thrombotic events in some studies may exaggerate some of the incidence rate. Chemotherapy-related CVA is overall less common than coronary artery thrombosis. Medications with the highest rates of CVA or transient ischemic attack (TIA) include cisplatin [14, 27], ponatinib [26], and lenalidomide [29]. PAD has been reported as a significant complication of only a few medications. The most significant medications include nilotinib [22, 49–51] and ponatinib [22, 26] with incidence of occlusive PAD up to

25 and 48%, respectively. The occlusive PAD associated with these Bcr-Abl TKIs can occur in patients without any traditional cardiovascular risk factors and may be severe and progressive despite cessation of therapy [51].

Risk factors for arterial thrombosis

Thrombosis can occur in any vessel leading to complications such as myocardial infarction, stroke, or limb ischemia as described above. The factors of Virchow's triad, endothelial injury, stasis, and hypercoagulability, contribute to the development of both venous and arterial thrombi; however, platelet activation in the setting of pre-existing disease, such as atherosclerosis and vasculitis, appears to be crucial for the development of arterial thrombosis [56, 57]. Many risk factors, such as age, smoking, hypertension, and diabetes, are common to both venous and arterial thrombi [56, 57]. While thrombophilic disorders, such as factor V Leiden and prothrombin G20120A, are important risk factors for venous thrombosis, they carry a much lower risk for arterial thrombosis. Lupus anti-coagulant and hyperhomocysteinemia are notable exceptions that are well-known to cause arterial thrombi [57].

Cancer is a hypercoagulable state associated with a 7-fold increase in venous thromboembolism; however, the association with arterial thromboembolism (ATE) is less well established [58, 59]. Case reports of patients presenting with arterial thrombosis as the first sign of an occult malignancy or progression of an early-stage cancer [59, 60] suggest that cancer may be an independent risk factor for arterial thrombi. A case report of three patients with acute arterial thrombosis in the setting of a new malignancy additionally highlighted that the thrombotic events occurred with no signs of a non-neoplastic-associated hypercoagulable state or atherosclerosis [61]. Some malignancies, such as polycythemia vera and multiple myeloma, are commonly associated with arterial thrombosis [57, 62]. In a large population study in Sweden, patients with multiple myeloma were found to have an increased risk of ATE at 1, 5, and 10 years after the initial diagnosis with hazard ratios [95% confidence intervals] as follows: 1.9 [1.8–2.1)], 1.5 [1.4–1.6], and 1.5 [1.4–1.5], respectively [63].

Radiation is a common part of cancer treatment and an important modifier of arterial thrombosis risk. The earliest effects of radiation therapy are seen on the vascular endothelium [64], which is vulnerable to injury. Vascular fibrosis is a later findings that can affect any layer of the vessel wall [65]. Radiation vasculopathy is associated with accelerated atherosclerosis [66•]. For example, in a cohort of patients treated with radiation therapy for Hodgkin's lymphoma, the prevalence of CAD based on CT scans was 39% two decades after treatment [67]. In a large population-based study of breast cancer patients in Sweden and Denmark, prior radiotherapy was associated with a significant increase in risk of major coronary events within a few years of treatment. This risk persisted for decades after radiotherapy and correlated linearly with the mean radiation dose (7.4% increase in risk per 1 Gray of radiation) [68]. Similarly, PAD is a risk for patients who undergo extracardiac radiation, although this has been less well studied compared to CAD. Radiation therapy is also associated with a higher risk of stroke. Dorresteijn et al. [69] reported a 12% 15-year cumulative risk of ischemic stroke following radiation for head and neck tumors. Plummer et

al. reported that head and neck radiotherapy at least doubled the risk of transient ischemic attack/stroke [70, 71]. They suggest that both accelerated atherosclerosis and injury to the vasa vasorum contribute to carotid vasculopathy [70, 71].

Pathophysiologic mechanisms of arterial thrombosis in cancer

Virchow's triad

The classical concept of vascular thrombosis is that of Virchow's triad. Accordingly, a thrombus forms as a consequence of alterations of the blood contents (mainly platelets and coagulation factors), the vessel wall (mainly endothelium), and blood flow (mainly blood flow turbulence and stasis).

The first factor in Virchow's triad appears critical to thrombogenesis in cancer patients. There is evidence that platelet reactivity is increased in cancer patients and that there are higher circulating levels of platelet-specific products such as soluble P-selectin, platelet factor 4, thrombospondin, and beta-thromboglobulin [5]. An emerging body of evidence suggests that there is a bidirectional interactions between platelets and cancer cells where paraneoplastic cells activate platelets, and conversely, platelets themselves play a role in cancer propagation and metastatic spread through a process described as "tumor education." Direct interaction of platelets with tumor cells induces thrombocyte aggregation in experimental pancreatic, colorectal, and renal cell lines [72]. Our current understanding of the changes in platelet activation and coagulation factors in cancer is reviewed in the following section.

The second element of the Virchow's triad, the vascular wall, is also an important contributor to thrombosis in cancer patients. Cancer therapies have a direct influence on the vascular wall, especially the endothelial monolayer. Increased circulating levels of von Willebrand factor (vWf) have been described in cancer patients and may not only be a marker of endothelial injury like soluble E-selectin, but also a contributor to thrombosis by promoting platelet-platelet and platelet-subendothelium interaction. Loss of expression of thrombomodulin on the endothelial surface reduces the capacity to activate the anti-coagulant protein C thereby adding to the prothrombotic state. These dysfunctional changes of the endothelium are the consequence of the production of inflammatory cytokines such as tumor necrosis factor and interleukin (IL)-1. The circulating levels of a number of different cytokines are elevated in cancer patients [73]. Vascular endothelial dysfunction in the setting of malignancy not only causes procoagulant activity and decreased fibrinolytic activity [74]. This abnormal condition of the vasculature furthermore fosters inflammation, proliferation, and vasoconstriction, all of which contribute to the development and clinical presentation of ischemic vascular disease [75].

The third factor in Virchow's trial, blood flow, appears to play a minor role in the etiology of thrombosis in cancer patients [5]. It is rare that thrombosis would evolve as the consequence of external compression of a vessel due to an enlarging mass. Cancer patients do experience a decline in exercise tolerance and fatigue and assume a more sedentary lifestyle. Some patients may become quite bedridden which is a clear risk factor for venous thrombosis; however, this does not appear to play a critical role in arterial thrombosis.

Platelet activation and clotting factors

Cancer cells directly excrete a number of mediators of coagulation that likely significantly contribute to arterial thrombosis in cancer patients. Thrombin and other mediators excreted by cancer cells interact with platelet surface receptors via PAR-1 and PAR-4 receptors, P2Y12 receptor, and the thromboxane receptor. Secretion of matrix metalloproteinases (MMPs) and IL-6 have been shown to activate platelets directly [76, 77]. In breast cancer cell lines, secreted MMPs led to platelet activation, a change in shape to form pseudopodia, and an increase in the concentration of activated GPIIb/IIIa surface receptors, which subsequently bind with fibrinogen and form stable platelet aggregates [78]. A specific study of human small cell cancer cell lines revealed in vitro induction of platelet aggregation through direct cellular interactions observed under electron microscopy in small cell lung cancer and indirect cellular interactions via secreted thrombin and ADP mediators in non-small cell lung cancer [69]. In vitro, cancer cells can activate platelets by releasing stimulating factors such as ADP and thromboxane A2 [5].

Studies of patients with melanoma and mouse models of melanoma demonstrated that vWF plays a role in platelet aggregation and recruitment. Tumor-derived VEGF secretion mediates endothelial cell activation, promotes vWF expression in the tumor vessel lumen that then promotes platelet recruitment and atheroembolism [79]. A similar mouse xenograph of four different human pancreatic cell lines found two lines expressing known thrombogenic entities tissue factor (TF) and release TF-positive microparticles [80].

Other procoagulants produced by cancer cells that are of importance in shifting the balance between coagulation and fibrinolysis include fibrinogen and plasminogen activator inhibitor. Deficiencies in molecules such as anti-thrombin, proteins C and S, and tissue plasminogen activator also contributes to the development of arterial thrombosis [5].

Pathophysiologic mechanisms of treatment-related thrombosis

In addition to the milieu of the cancer environment, a number of chemotherapeutics have a detrimental effect on the function and viability of endothelial cells [81]. As mentioned above, there are many chemotherapeutic agents associated with thrombosis; however, the most classical illustration is found in the group of VEGF inhibitors [22].

VEGF is the central growth and survival factor for endothelial cells. Inhibition of the VEGF signaling pathway can therefore have profound cardiovascular effects including progression of atherosclerosis, provocation of ischemia, and thrombotic events. Binding of the VEGF receptor signals into the nitric oxide (NO) pathway, which is crucial for endothelial and vascular health. In cell culture experiments, pan-VEGF receptor inhibitor treatment reduced NO production in endothelial cells due to uncoupling of endothelial NO synthase, which was related to induction of mitochondrial oxidative stress [82]. Inhibition of the VEGF signaling pathway can leave an exposed endothelium due to impaired cell regeneration and may alter endothelial fluid shear stress sensing leading to vascular injury and thrombosis [83]. In addition to the effect on endothelial cell health, VEGF inhibitor-related hypertension likely further increases the risk of cardiovascular events [83].

VEGF receptor inhibitors decrease NO production, although with a mechanistic twist [82]. In an experimental model, pan-VEGF receptor inhibition significantly increased the extent of disease in mice prone to the development of atherosclerosis [82]. This was associated with a significant reduction in proliferating cell count but not with a reduction in capillary tube count or reduction in parameters of plaque vulnerability. Accordingly, VEGF inhibitor therapy may lead to a more gradual increase in atherosclerotic plaque burden, which may not become clinically evident for years, in contrast to thrombotic events that emerge acutely.

A second group of drugs that has recently been shown to increase the risk of vascular events are the Bcr-Abl inhibitors which are used in hematologic malignancies such as chronic myeloid leukemia [22]. The c-Abl signaling pathway operates in synergy with the VEGF signaling pathway and is important for the survival of endothelial cells. Inhibition of both pathways simultaneously should thus be greatly detrimental, as was seen with the ponatinib. In an unprecedented manner, ponatinib causes arterial more than venous vascular events including acute myocardial infarction, stroke, acute mesenteric ischemia, and limb ischemia. Some cases revealed such profoundly accelerated atherosclerosis, especially of the lower extremities, that a new term was coined: “progressive arterial occlusive disease.” The same phenomenon, but not as frequent, was also seen with nilotinib. This drug differs in its TKI target spectrum, and analyses had not shown an inhibition of VEGF receptor domains [84]. However, recent studies made the exciting discovery that nilotinib downregulates the expression of VEGF receptor 2 and behaves similarly to an angiogenesis inhibitor [85]. A meta-analysis from Sweden suggests that dasatinib also increases the risk of MI and stroke, pointing towards a class effect. How to best risk-assess and monitor these patients is currently unknown though proposals have been made.

Diagnosis of arterial thrombosis

Arterial thromboembolism often has an acute or subacute presentation with marked reduction in blood flow leading to critical ischemia and infarction of the supplied organ. The typical symptoms depend on the affected organ: chest pain for CAD, limb pain for PAD, or neurologic deficits for stroke. The overall diagnostic and treatment strategies center on the goal to restore blood flow as soon as possible. Invasive angiography is often pursued since it can quickly diagnose an occlusive thombus and enable revascularization. However, in non-emergent cases or when the diagnosis is unclear, noninvasive imaging such as CTA or MRA is often appropriate.

The classic definition of MI (type I) includes chest pain, ECG changes, and abnormal cardiac biomarkers caused by arterial thrombosis, usually in the setting of atherosclerotic disease. Type II MI is defined as myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply such as coronary spasm, hypotension, anemia, and coronary embolism [86]. Type II MI represents a significant proportion of ACS events in cancer patients. It can be difficult to clinically distinguish between the two types of MI, and therefore noninvasive functional testing or invasive coronary angiography may be indicated in this scenario.

Treatment considerations

Anti-platelets and percutaneous vascular interventions

Anti-platelet agents are central to the treatment of arterial thrombosis in both patients with and without cancer. However, careful consideration about the bleeding risk is needed because thrombocytopenia is common in cancer patients [87]. In a study of patients presenting with acute coronary syndrome, baseline thrombocytopenia was associated with a higher rate of complications compared to patients without thrombocytopenia (30 day death rate 6.2 versus 2.1%, major bleeding 11.9 versus 7%, major cardiac events 9.6 versus 5.2%, major cardiac events plus major bleeding 18.5 versus 10.8%) [88]. A recently published expert consensus statement from the Society of Cardiovascular Angiography and Interventions recommends that aspirin can be given if the platelet count is > 10,000, and DAPT with aspirin and clopidogrel is reasonable for platelet counts between 30 and 50,000. Other newer P2Y12 receptor inhibitors such as ticagrelor and prasugrel which have a higher bleeding rate should generally be avoided below a platelet count of 50,000 [66•]. McCarthy et al. on the other hand, recommend a more conservative approach and advise against all anti-platelet agents and PCI in patients with a platelet count < 50,000 [89].

Revascularization is imperative in the setting of critical ischemia or infarction. Depending on the territory at risk, treatment options include thrombectomy (as in the case of PAD or stroke), percutaneous coronary intervention, bypass surgery, or percutaneous peripheral angioplasty. Based on the SCAI expert consensus, there is no platelet count limit for diagnostic left heart catheterization [66•, 90]. DAPT should be continued for the least safe time if platelet count is < 50,000 (meaning 4 weeks for BMS or 6 months for drug-eluting stents). In patients who have a platelet count < 30,000, a multidisciplinary discussion involving cardiology and oncology is recommended prior to pursing PCI [66•].

Coronary stent endothelialization

An important question is how chemotherapeutic agents may influence the endothelialization of stents and the risk of stent thrombosis. One study so far has found a 7-fold higher risk of stent thrombosis in cancer patients who had undergone BMS [12]. This observation and the un-derlying mechanisms remain to be confirmed. However, it is conceptually conceivable that cytostatic and cytotoxic chemotherapeutics impair stent endothelialization. This would affect the ingrowth of both surrounding endothelial cells and circulating progenitor cells [91]. Circulating progenitor cells are the main source for endothelialization of stents [92], and patients with stent thrombosis have lower endothelial progenitor colony forming unit capacity [93]. Endothelial and circulating progenitor cell levels are suppressed in cancer patients, especially in the acute treatment phase and remain lower in those receiving VEGF-directed therapies [94].

In a large animal model, VEGF significantly improved re-endothelialization, and the effect was even more pronounced under conditions of hypercholesterolemia [95]. Interestingly, VEGF also reduces excess neointima proliferation and restenosis [95]. Similar to the discussion above, VEGF is an important signaling factor for endothelial cell health in

patients who undergo PCI. Cancer patients are at risk of arterial vascular events due to interference of this pathway during administration of drugs cytotoxic to endothelial cells.

Role of anti-platelet therapy in metastatic spread

The role of platelets in metastatic spread leads to the hypothesis that anti-platelet agents will decrease tumor progression [96, 97]. There is evidence that P2Y12 inhibitor ticagrelor reduced metastatic burden in murine models of melanoma and breast cancer [98]. In prostate cancer, aspirin use after diagnosis may only improve prostate cancer mortality in patients with high-risk cancer [99]. In a large population-based cohort study and a meta-analysis of multiple-cohort patients, starting low-dose aspirin therapy after diagnosis of colorectal cancer was not associated with a reduction in colorectal cancer-specific mortality [100, 101]. Overall, evidence suggests that a personalized approach should be used, rather than routine treatment with anti-platelet therapy, while the role of anti-platelet agents in slowing malignant progression remains unclear.

Future avenues

There are numerous opportunities for further investigation into preventive strategies for arterial thromboembolic disease in cancer patients. One important question that should be addressed is whether anti-platelet or anti-coagulation can be effective in the prevention of arterial thrombosis. Aspirin, for example, has been shown to decrease the rates of arterial thrombosis in polycythemia vera and multiple myeloma [102, 103]. However, whether we can prevent arterial thrombi in other cancers or prevent treatment-related thrombosis is unknown. Lipid-lowering and anti-inflammatory statin medications are protective against arterial thrombosis in the setting of atherosclerotic disease and have even been shown to decrease venous thromboembolism in patients with cancer [104]. Nonetheless, their efficacy in cancer-related arterial thrombosis is unknown. PET-CT scans, which are already done as part of cancer staging, may help identify at least some of the patients who should be started on a statin prior to chemotherapy based on the presence of coronary and vascular calcium, which may potentially be predictive of cardiac events [105]. However, the decision to initiate statin should also take into account the cancer type and the specific oncologic treatment [105]. Several recent/ongoing studies are starting to investigate the use of aspirin, statins, biomarkers, and novel anti-coagulants in the prevention and treatment of cancer patients with thromboembolic disease [106–110]. Optimal surveillance strategies for arterial thromboembolic disease remain unclear. There are many imaging modalities for identifying arterial disease; however, which patients should be screened and at what time interval is unknown and warrants further investigation. A personalized and multidisciplinary approach considering the patient’s traditional cardiovascular risk factors as well as the specific risks of the cancer type and oncologic treatment is recommended until more studies and guidelines are developed.

In regard to the potential mechanistic crossover of treatments that may contribute to the genesis of both cardiac and oncologic disease, interest has been generated recently with the CANTOS trial. The agent studied, canakinumab, is an anti-inflammatory, monoclonal antibody targeting interleukin-1beta that has recently attracted attention within the cardiology

community after demonstrating that it decreases the rate of myocardial infarction in patients with coronary artery disease. This effect occurred irrespective of the cholesterol level which helped prove the inflammatory hypothesis of atherothrombosis [111]. This discovery has opened the cardiology field to the pursuit of novel medications targeting inflammatory pathways. Cancer is a highly inflammatory condition; therefore, this or similar drugs may also prove to be beneficial in the prevention and treatment of cancer-related arterial thrombosis. Canakinumab may also be an appealing medication to study given the unexpected finding that canakinumab was associated with significantly lower rates of lung malignancy. This interesting observation requires further study but continues to demonstrate a possible commonality between the potential triggers of both cardiovascular disease and cancer [111].

Conclusion

In conclusion, malignancy-related arterial thrombosis results in an increased risk of morbidity and mortality. With cardiac events that may occur during cancer treatment, whether it is cancer or treatment induced, further research is needed to further delineate thrombosis risk by treatment agent and types of cancer. Collaboration between cardiology and oncology is essential in providing evidence-based and individualized care in treating these patients; this involves ongoing discussions of treatment strategies of such events, as well as the risks and benefits of continuing chemotherapies that may be contributing to the thrombotic events. National, multi-institutional registries tracking these events, as well as potential randomized controlled trials in looking at pharmacologic—anti-platelet and anti-coagulant—and invasive therapies, will advance our understanding in attenuating long-term thrombosis risk and potentially improve long-term outcomes in both cardiovascular and oncologic survival.

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Papers of particular interest, published recently, have been highlighted as:

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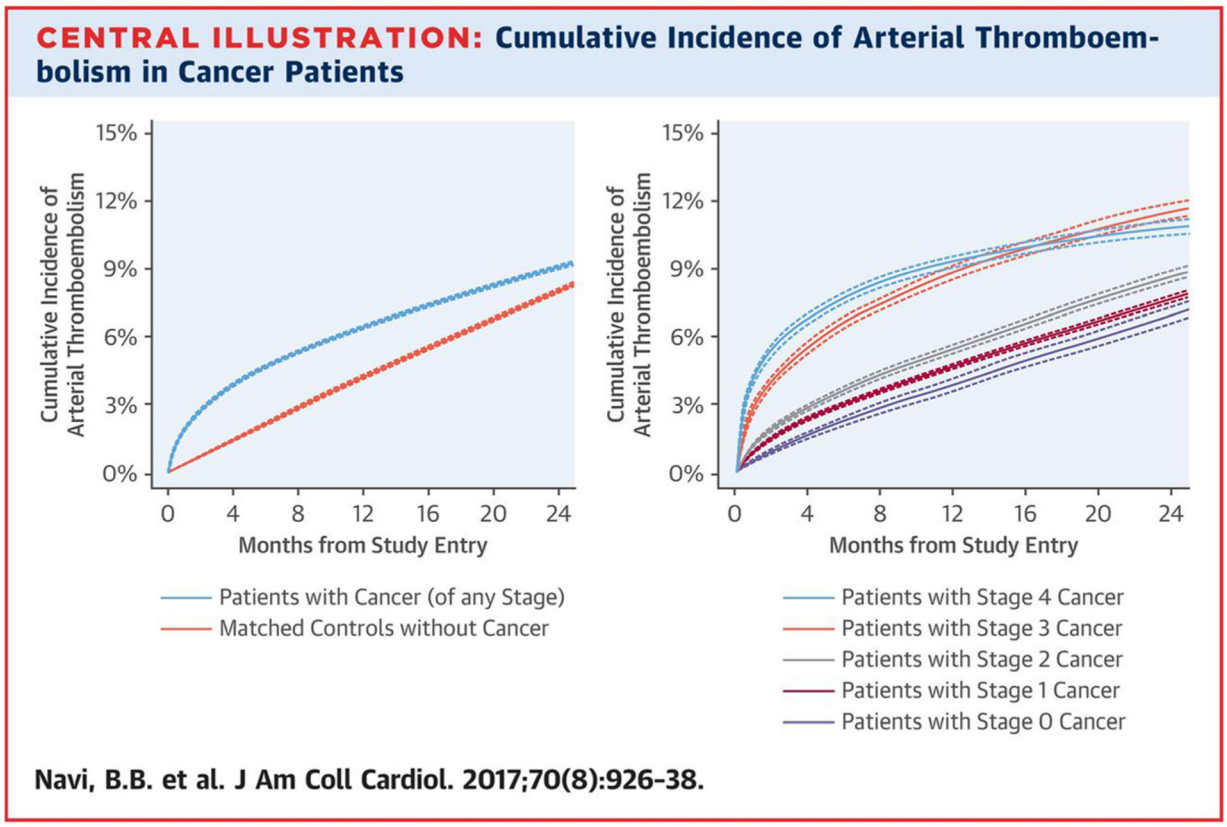

Fig. 1.

*Cumulative incidence of arterial thromboembolism (composite of myocardial infarction and ischemic stroke) in patients with cancer compared to matched control patients (left panel) and when stratified by cancer stage at the time of cancer diagnosis (right panel). Competing risk survival statistics were used to calculate incidence. Dashed lines are used to indicate 95% confidence intervals. Reprinted from Navi et al., J Am Coll Cardiol 2017;70(8):926–38, with permission from Elsevier.

Table 1.

Arterial thromboembolic event rate for various chemotherapeutic agents

Medication class	Medication name	Incidence[a]	Event type
Coronary artery events			
Platinum-based agents [14, 27]	Cisplatin	1.6–8.7%	Myocardial infarction
Platinum-based agents [28]	Cisplatin	3.1-fold increase	Myocardial infarction
Immunomodulatory drugs [29]	Lenalidomide + dexamethasone	1.98%	Myocardial infarction
VEGF inhibitor [16, 18, 22, 30]	Bevacizumab	0.6–2%	Myocardial infarction/acute Coronary syndrome/cardiac ischemia
VEGF TKI [31]	Sunitinib	11%	Heart failure or myocardial infarction
VEGF TKI [22]	Pazopanib	2%	Myocardial infarction
VEGF TKI [32, 33]	Sorafenib	3–4.9%	Cardiac ischemia or infarction
Bcr-Abl TKI [22]	Nilotinib	7.50%	Acute coronary syndrome
Bcr-Abl TKI [26, 34]	Ponatinib	1–12%	Myocardial infarction
Fluoropyrimidine [35, 36]	Capecitabine	0.5–9%	Angina pectoris, myocardial ischemia, myocardial infarction, acute coronary syndrome
Fluoropyrimidine [37]	Capecitabine	1.90%	Cardiotoxicity
Fluoropyrimidine [35, 38, 39]	5-FU	0.7–8%	Myocardial infarction, angina/cardiac chest pain
Fluoropyrimidine [37, 40–42]	5-FU	1.2–18%	Cardiotoxicity
Fluoropyrimidine [43]	Capecitabine +5-FU	0–2%	Myocardial infarction/cardiogenic shock/cardiac arrest
Taxol [44, 45]	Paclitaxel	0.26–5%	Myocardial infarction/myocardial ischemia
Taxol [46]	Paclitaxel	5%	Arrhythmia, conduction blocks, cardiac ischemia
Aromatase inhibitors [47]	-	4.20%	Cardiovascular event
Cerebrovascular accident			
Platinum-based agents [27]	Cisplatin	8.70%	Cerebrovascular accident
Platinum-based agents [14]	Cisplatin + gemcitabine	0.80%	Cerebral ischemic stroke
Thalidomide analogue [29]	Lenalidomide + dexamethasone	3.40%	Cerebrovascular accident
VEGF inhibitor [16,18, 22]	Bevacizumab	1.1–1.9%	Ischemic stroke/cerebrovascular accident, transient ischemic attack
VEGFR inhibitors [33]	Sorafenib	1.50%	Central nervous system ischemia
VEGFR inhibitors [48]	Pazopanib	1%	stroke/transient ischemic attack
Bcr-Abl TKI [26]	Ponatinib	6%	Cerebrovascular occlusion
Peripheral artery disease			
Platinum-based agents [14]	Cisplatin + gemcitabine	5.6%	Iliac artery embolism
Bcr-Abl TKI [22, 49–51]	Nilotinib	1.1–25%	Peripheral artery (occlusive) disease, visceral arteries and limb ischemia
Bcr-Abl TKI [22, 26]	Ponatinib	8–48%	Peripheral arterial occlusive events, visceral arteries and limb ischemia
All arterial thromboembolic events			
Platinum-based agents [13–15]	Cisplatin	1.4–8.3%	Arterial thromboembolic event

Medication class	Medication name	Incidence[a]	Event type
Immunomodulatory drugs [52, 53]	Thalidomide	4.5–12.5%	Arterial thromboembolic event
VEGF inhibitor [16–19]	Bevacizumab	1.7–3.8%	Arterial thromboembolic event
VEGF inhibitor [20]	Bevacizumab + chemotherapy	5.5 events per 100 person-years	Arterial thromboembolic event
VEGF TKI [21]	Sorafenib	1.7%	Arterial thromboembolic event
VEGF TKI [22]	Sorafenib (RR is compared to bevacizumab)	RR 2.3	Arterial thromboembolic event
VEGF TKI [21, 23]	Sunitinib	1.3–4.1%	Arterial thromboembolic event
VEGF TKI [22]	Sunitinib (RR is compared to bevacizumab)	RR 5.9	Arterial thromboembolic event
VEGF TKI [24, 25]	Pazopanib	3–4%	Arterial thromboembolic event
VEGF TKI [22]	Pazopanib (RR is compared to bevacizumab)	RR 4.6	Arterial thromboembolic event
Bcr-Abl TKI [26]	Ponatinib	20%	Arterial thromboembolic event
Selective estrogen-receptor modulator [54]	Tamoxifen + chemotherapy	1.60%	Arterial thromboembolic event

VEGF vascular endothelial growth factor, *TKI* tyrosine kinase inhibitor, *FU* fluorouracil, *RR* relative risk, *HR* hazard ratio, *CI* confidence interval

[a]Unless otherwise noted