Title
Vascular Toxicities of Cancer Therapies: The Old and the New--An Evolving Avenue.

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Abstract—Since the late 1990s, there has been a steady decline in cancer-related mortality, in part related to the introduction of so-called targeted therapies. Intended to interfere with a specific molecular pathway, these therapies have, paradoxically, led to a number of effects on their intended cancer tissue or molecular targets. The latest examples are tyrosine kinase inhibitors targeting the Philadelphia Chromosome mutation product, which have been associated with progressive atherosclerosis and acute vascular events. In addition, agents designed to interfere with the vascular growth factor signaling pathway have vascular side effects ranging from hypertension to arterial events and cardiomyocyte toxicity. Interestingly, the risk of cardiotoxicity with drugs such as trastuzumab is predicted by preexisting cardiovascular risk factors and disease, posing the question of a vascular component to the pathophysiology. The effect on the coronary circulation has been the leading explanation for the cardiotoxicity of 5-fluorouracil and may be the underlying mechanism of presentation of apical ballooning syndrome with various chemotherapeutic agents. Classical chemotherapeutic agents such as cisplatin, often used in combination with bleomycin and vinca alkaloids, can lead to vascular events including acute coronary thrombosis and may be associated with an increased long-term cardiovascular risk. This review is intended to provide an update on the evolving spectrum of vascular toxicities with cancer therapeutics, particularly as they pertain to clinical practice, and to the conceptualization of cardiovascular diseases, as well. Vascular toxicity with cancer therapy: the old and the new, an evolving avenue. (Circulation. 2016;133:1272–1289. DOI: 10.1161/CIRCULATIONAHA.115.018347.)

Key Words: angina pectoris ▪ chemotherapy ▪ complications, cardiovascular ▪ coronary vasospasm ▪ drug therapy ▪ endothelial cells

"Is it time for oncologists to get to know their cardiologists?" was an editorial rhetoric almost 10 years ago and seems to be an even timelier question now.1 Indeed, the spectrum of therapies and the population of patients have broadened considerably over the past decade and so have the profile and consequences of cardiovascular side effects. Accordingly, the cardiovascular care of patients who have cancer has received increasing attention, and demands in this area have and will continue to grow considerably. Although the mechanisms, monitoring, and management of cardiotoxicities have received broad attention, vascular toxicities remain underrecognized. In addition, the development of new chemotherapeutic drugs bears the risk of vasotoxicities that are yet to be identified and may not be realized with short-term follow-up periods. The purpose herein is to provide an updated overview of the clinical manifestations and pathomechanisms of chemotherapy-induced vascular toxicities. Furthermore, novel insights into vascular biology and pathology from targeted cancer therapies will be presented, and vascular toxicity aspects of classical cardiotoxic drugs (chemo-vaso-cardio interaction), as well.

Vascular Toxicities With Cancer Therapies
Chemotherapy-related vascular toxicity presents in a number of different ways as outlined in Figure 1 and further detailed in the following.

Systemic Hypertension
New-onset or worsening systemic hypertension can be noted with numerous chemotherapeutic agents (Table) and is particularly common with drugs inhibiting the vascular endothelial growth factor (VEGF) signaling pathway. Bevacizumab was the first agent in this class with a 70% risk of hypertension, 20–30% higher than expected.2 Intensification of therapy (hypertension grade 3, see online-only Data Supplement Table I), however,
was required only in 10% to 20% of patients, and life-threatening hypertensive crises were rare (≈1%). As pointed out in meta-analyses (online-only Data Supplement Table II), the incidence of hypertension seems to be even higher with the newer-generation drugs.3,4 Furthermore, there is variation among the different cancer types (potentially higher in patients who have renal cell carcinoma) and certain ethnic populations (eg, in Japanese patients in axitinib trials: 84% overall incidence of hypertension, 70% high grade).3 The primary at-risk groups, however, are those with preexisting hypertension, advanced age (≥60–65 years), history of smoking, hypercholesterolemia, or obesity (Figure I in the online-only Data Supplement).6,7 Increases in blood pressure are in the order of 10 to 20 mm Hg systolic and 5 to 15 mm Hg diastolic and most pronounced during the first few cycles of therapy, and in fact can occur within hours of therapy initiation, especially with tyrosine kinase inhibitors (TKIs).2

The mechanisms by which VEGF inhibitors increase blood pressure remain incompletely understood.8 Changes in systemic vascular resistance, secondary to endothelial dysfunction and capillary rarefaction, are potential mechanisms.2 This is in keeping with the well-documented effects of VEGF in angiogenesis and nitric oxide (NO) production by endothelial NO synthase, with NO being crucial for normal endothelial function, vascular homeostasis, and angiogenesis.8 Activation of the endogenous endothelin system might be an additional contributing factor, whereas clinical studies have not confirmed a role for the renin-angiotensin system.

Mammalian target of rapamycin inhibitors are another class of chemotherapeutic agents that have been associated with hypertension. The risk is higher with everolimus (overall, 4%–30%; hypertensive crisis, 1%) than temsirolimus (overall <10%) and the mechanisms are not well defined. These drugs also raise the cholesterol, triglyceride, and glucose levels and thus lead to an overall unfavorable cardiometabolic profile.9

Management
It is recommended that patients considered for therapy with agents that have a known hypertension risk undergo a thorough evaluation of their baseline status (Figure I in the online-only Data Supplement). Control of hypertension is particularly advisable to prevent new-onset or worsening myocardial ischemia and heart failure in these patients. Once therapy with these agents is initiated, blood pressure should be monitored regularly with closer surveillance in the early stages (Figure II in the online-only Data Supplement).10 No clinical trial data are available to guide recommendations of antihypertensive therapies in patients with cancer, and, thus, the Eighth Joint National Committee guidelines should be followed.11 Angiotensin-converting enzyme inhibitors are effective in mild hypertension and also decrease proteinuria, which may coexist in these patients (along with renal dysfunction). Calcium channel blockers might be more effective, but nondihydropyridines should be avoided because they inhibit cytochrome P450 3A4, which can result in higher levels of VEGF inhibitors.8 In cases of severe, resistant hypertension, therapy should be interrupted, which (usually) promptly and effectively decreases blood pressures.

Pulmonary Hypertension
Dyspnea in patients with cancer encompasses a broad differential and can be provoked by cancer therapies. Dasatinib, a TKI of BCL-ABL, used in patients with Philadelphia Chromosome-positive leukemias, is the most intriguing example of a chemotherapeutic that can induce precapillary pulmonary hypertension. Increases in pulmonary arterial pressures (average mean pulmonary pressure, 46 mm Hg; average right ventricular systolic pressure, 65 mm Hg) can occur in up to 11% of patients on dasatinib.12,13 Importantly, although improving after cessation of therapy, dasatinib-induced pulmonary hypertension may not be fully reversible. In the original
### Table. Chemotherapeutic Agents With a Prominent Vascular Side Effect Profile

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AMI indicates acute myocardial infarction; DVT, deep vein thrombosis; HTN, hypertension; mTOR, mammalian target of rapamycin; PAD, peripheral arterial disease; PE, pulmonary embolism; Pulm, pulmonary; and VEGF, vascular endothelial growth factor.
series of 9 patients, pulmonary hypertension treatment was initiated in 3 patients with continuation of endothelin receptor antagonists in 2 of these. Two patients died during follow-up, one with persistent severe pulmonary hypertension, functional class III dyspnea and right ventricular dilation, and one with functional improvement but sudden death.12

Experimentally, the combination of a VEGF receptor 2 inhibitor with chronic hypoxia results in reproducible pulmonary hypertension.14 Furthermore, VEGF receptor-2 deficiency, even confined to endothelial cells, impairs vascularization and resolution of intrapulmonary artery thrombi.15 Combined with the right substrate, this may lead to chronic thromboembolic pulmonary hypertension. Rho kinase–mediated vasoconstriction contributes to severe occlusive pulmonary hypertension under these conditions.16 Importantly, not all TKIs, VEGF signaling pathway directed or not, are associated with pulmonary hypertension, probably because of remarkable differences in the molecular targets. Dasatinib yields the best in vitro and in vivo results with regard to the treatment of pulmonary hypertension because of the concomitant inhibition of platelet-derived growth factor (PDGF) receptor and Src kinases.17 Other receptor tyrosine kinases (c-kit, fibroblast growth factor-2, and epidermal growth factor receptor) have been implicated in the pathogenesis of pulmonary hypertension; however, paradoxically, dasatinib is a potent inhibitor of these.13 On the contrary, imatinib, inferior in experimental studies, improves pulmonary hypertension and exercise tolerance in clinical practice.14 The definite mechanisms of dasatinib-induced pulmonary hypertension remain unknown, but its association with exudative pleural effusions, paracardial effusion, and lymphocytic accumulations in pleural and bronchoalveolar lavage and biopsies point toward a potential immune mechanisms.19

Another chemotherapeutic drug notoriously associated with pulmonary hypertension is bleomycin. The overall risk is ≈10%, emerging gradually over the course of therapy and even years later.20 A distinctive feature is the development of pulmonary fibrosis as a consequence of the stimulation and transformation of fibroblasts into collagen-producing myofibroblasts by activated alveolar macrophages and epithelial cells in a response-to-injury pattern.20 The inflammatory response is tied to the stimulation of oxidative stress and alternation in NO signaling, reminiscent of atherosclerosis in a number of ways. Accordingly, statins have been shown to ameliorate bleomycin-induced lung injury as have Rho kinase inhibition, endothelin receptor antagonism, arginase inhibition, and provision of inhaled or even dietary NO, and sildenafil.21–28

Finally, interferon-α can induce pulmonary vasculitis and pulmonary hypertension for unknown reasons.20 Immune mechanisms are discussed among others, similar to the discussion on the effects of interferon-α on the peripheral arterial vasculature. Although not necessarily vascular in nature, it should not be left unmentioned that mammalian target of rapamycin inhibitors can induce a noninfectious pneumonitis.30

Management

It is recommended that all patients undergo evaluation for signs and symptoms of underlying cardiopulmonary disease before initiation and during treatment, especially with the mentioned drugs. Importantly, patients can become symptomatic at any time during and even years after their treatment. Dyspnea, hypoxia, cough, fatigue, and abdominal and lower extremity edema should prompt an immediate evaluation, which should include an ECG, chest x-ray, and echocardiogram. Contrast and high-resolution chest computed tomographies are useful to address a number of potential disease processes such as pulmonary embolism and pneumonitis, and pulmonary function tests are useful to define the functional nature of a pulmonary disease process. Depending on the findings, these patients should be referred to a specialist. Overall, pulmonary hypertension should be managed in keeping with published guidelines.31

Typical and Atypical Chest Pain

Similar to dyspnea, chest pain can have numerous etiologies in patients with cancer, including pulmonary embolism, pericardial irritation, and myocardial ischemia. The latter can be caused by a number of chemotherapeutic agents. The classical example is 5-fluorouracil (5-FU), which causes chest pain in 1% to 18% of patients exposed, and its oral produg capcitabine at a 50% lower rate. The onset can be rather quick (as systemic peak levels are reached) and relates to an alteration in vascular reactivity.32,33 The types of presentation include effort angina and abnormal noninvasive stress testing,34 but also resting and variant angina. This relates to the fact that these drugs primarily alter molecular signaling pathways that control vascular smooth muscle cell tone and induce vasoconstriction.35

Another class of chemotherapeutic agents known to induce similar types of chest pain are the taxanes, namely paclitaxel at an incidence of 0.2% to 4%,36–38 Similar to 5-FU, vasoconstriction (spasm) has been considered to be a key mechanism. In distinction, however, cardiac rhythm disturbances are more common with taxanes.36

Cisplatin, even more so in combination with bleomycin and vinca alkaloids, can provoke chest pain presentations at an incidence as high as 40%.39–44 The propensity of these drugs to injure the endothelium is well established, and endothelial dysfunction is therefore the key mechanism of altered vasoreactivity with these drugs.45

VEGF signaling pathway inhibitors are another class of drugs well known to be associated with angina at an incidence of 1% to 15%.

Again, endothelial dysfunction likely plays an important role, because inhibition of VEGF receptor signaling impairs stimulation of endothelial NO synthase activity via the Akt/PKB pathway.46 Moreover, endothelial NO synthase uncoupling may occur with an increase in oxidative stress, activation of the endothelin system, furthering the propensity toward abnormal vascular reactivity and structure.47–50 In addition, interference with Rho kinase activation in vascular smooth muscle cells might contribute to potentially profound vasospasms as reported especially for sorafenib.51–53 Accelerated atherosclerosis has been observed in patients receiving treatment with sorafenib, progressing from a normal coronary angiogram to critical subocclusion of the left main over the course of only 4 years.54 These dynamics are confirmed by

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On the other hand, bevacizumab reduced neovascularization and growth of established plaques similar to other antiangiogenesis inhibitors in experimental models. Thus, VEGF signaling pathway inhibitors may be unique in their capacity to alter vasoreactivity and the atherosclerotic disease process with potentially important differences between them.

Last but not least, patients with cancer can also develop signs and symptoms of myocardial ischemia as a consequence of coronary artery compression by various cardiac and noncardiac tumors. Malignant tumors, even from the left atrium, can cause coronary compression that may lead to myocardial infarction. As another example, the left main stem can be involved in the setting of mediastinal tumors such as lymphoma. Noncompressive encasement of the right coronary artery in the right ventricular groove has been described with mediastinal diffuse large B-cell lymphoma and thymoma, so-called floating artery sign. True invasion in the coronary arteries should raise suspicion for angiosarcoma.

Management

At present, there are no guideline-based recommendations for the evaluation and management of patients with cancer at risk for the outlined side effects. The Society for Cardiac Angiography and Intervention, however, recently commissioned a consensus effort in this area (Figure 2). Assessment of baseline cardiovascular history and risk is the key first step, and any potentially modifiable risk factor and disease state should be optimized before proceeding with any potentially vasotoxic therapy. A distinction is to be made (proposed herein similar to the one for cardiotoxicity) between drugs with a transient and mainly functional risk (type II chemotherapy–related vasotoxicity, eg, 5-FU) and those with a potentially long-term and structural risk (type I chemotherapy–related vasotoxicity, eg, nilotinib and ponatinib). The goals, modes, and duration of testing vary accordingly. They are to be more functionally directed before and during therapy for type II agents, eg, peripheral vasoreactivity testing by Endo-PAT, whereas they are to include structural assessments and their consequences for type I agents, eg, coronary angiogram and cardiac stress tests. Although every patient is unique and needs individualized care, a general outline of an evaluation sequence is presented in Figure 2.

Given the predisposition to coronary vasoconstriction, especially with type II agents, administration of nitroglycerin and calcium channel blockers is the best initial diagnostic and therapeutic step (Figure III in the online-only Data Supplement). Subsequently, the decision is to be made on further testing for structural heart disease. A more comprehensive and definitive assessment is usually advisable for patients at risk of developing progressive atherosclerosis. The most complete cardiovascular risk and disease assessment is also recommendable if further treatment with the same or a similar drug is considered and the patient is expected to derive a significant oncological benefit from it. Under those circumstances, the goal is to facilitate the continuation of chemotherapy while managing and mitigating cardiovascular disease risk and side effects. Moreover, a more comprehensive...
imaging evaluation is recommended if there are any concerns of coronary artery compression.

The most effective preventive strategy is the avoidance of continuous and high-dose infusions for 5-FU and the reduction in chemotherapy dosing in general. Pretreatment with nitrates and calcium channel blockers before exposure to type II agents is another option. Because the underlying mechanisms of vascular toxicity with type I agents remain to be elucidated, no definite management recommendation can be given. Dual-antiplatelet therapy, statins, angiotensin-converting enzyme inhibitor, and amlodipine have been elected in selected cases.

**Acute Coronary Syndromes**

Acute coronary syndromes (ACS) can develop in patients who have cancer, encompassing the entire spectrum from unstable angina to acute myocardial infarction (AMI) and even sudden cardiac death. As outlined above, a number of chemotherapeutic agents can alter coronary vasoreactivity and thus lead to resting, unstable angina presentations. The intensity and duration of vasoconstriction can even provoke myocardial infarction and arrhythmic complications such as ventricular tachycardia and fibrillation. This has been reported with 5-FU and capectabine (Figure III in the online-only Data Supplement). Profound and prolonged vasospasm has also been implied in ACS presentations of paclitaxel, gemcitabine, rituximab, and sorafenib. Other type II ACS/AMI scenarios can be induced by tachycardia, hypotension, hypoxia, and anemia in patients who have cancer with significantly reduced myocardial reserve because of coronary artery disease or potentially pathoanatomic variants such as myocardial bridging.

Type I ACS/AMI scenarios are also encountered as a consequence of the well-established types of plaque complications. Given the toxic effect of chemotherapeutic agents on the endothelial cells, there might be a greater propensity toward erosion in patients with cancer. A classic example is cisplatin, with and without bleomycin and vinca alkaloids. Single and even multivessel coronary thrombosis can be evident on angiography without any underlying atherosclerosis. Erosion as the leading mechanism is supported by experimental studies pointing out the induction of endothelial damage by thromboemboli via a patent foramen ovale, from the cardiac chambers and valves, and even tumor embolization.

Type I ACS/AMI mechanisms of acute coronary syndrome are to be considered for patients who develop signs and symptoms of myocardial ischemia or a combination thereof. Last but not least, other atypical mechanisms of acute coronary syndrome are to be considered in patients with cancer including spontaneous coronary artery dissection.

Whether there is any mechanistic overlap with ACS in patients the BCR-ABL–directed TKIs nilotinib and ponatinib remains ill-defined. Ponatinib at least has definite VEGF signaling inhibition properties and causes hypertension in nearly 70% of patients. In the few detailed case reports thus far, AMIs seemed to be the consequence of coronary artery obliteration in the presence of significant plaque development, but not necessarily typical plaque rupture with thrombotic occlusion similar to what has been reported in other vascular territories (Figure 3). In one of the larger retrospective series on nilotinib, ACS presentations were encountered in 6 patients (7.5%), occurring at any point in time during and even a month after treatment. Two of the 6 patients had an AMI, 1 with a fatal outcome, and 3 of the other 4 patients experienced recurrent events, 2 of which had undergone percutaneous coronary intervention.

Given a predisposition to a procoagulant state, in general, patients with cancer are also at risk for coronary artery occlusion by thromboemboli via a patent foramen ovale, from the cardiac chambers and valves, and even tumor embolization or a combination thereof. Last but not least, other atypical mechanisms of acute coronary syndrome are to be considered in patients with cancer including spontaneous coronary artery dissection.

Extrinsic compression by a tumor mass is usually a gradual phenomenon, but sudden growth could lead to unstable and acute presentations.

**Management**

Patients who develop signs and symptoms of myocardial ischemia should be immediately treated with nitroglycerin to alleviate any possible coronary vasoconstriction (see above). Cardiac catheterization laboratory is advisable to exclude any other concomitant process that could account for an ACS presentation (especially if high-risk features are present such as refractory angina, malignant arrhythmias, and shock) and to
guide treatment decisions. This can be done safely in most patients who have cancer despite anemia, thrombocytopenia, and coagulation abnormalities. Further management decisions are to be guided based on the findings. If uncertainty remains with regard to underlying coronary artery pathology, intravascular ultrasound and optical coherence tomography might be useful. The decision on percutaneous coronary intervention is to be made in the overall disease context. Aspirin may attenuate the ischemic event risk, at least with bevacizumab and especially in those ≥65 years and a prior history of an arterial thrombotic event (12.5% versus 22.9%), but at a 1.3 times higher risk of grade 3 and 4 bleeding events.81 In general, all patients should be treated with optimal guideline-directed therapy, unless there is a compelling prohibitive reason.

Apical Ballooning Syndrome (Stress or Takotsubo Cardiomyopathy)

Beyond the outlined typical scenarios of ACS, patients who have cancer can present with apical ballooning syndrome, precipitated by various factors.95 In fact, this entity might be relatively more common among patients who have cancer given the exposure to various and significant stressors. Moreover, this syndrome has been noted with the use of a number of chemotherapeutic agents, including 5-FU, capcitabine, cytarabine, axitinib, sunitinib, bevacizumab, rituximab, trastuzumab, and combretastatin.96–105 In a series of 38 patients with cancer and stress cardiomyopathy seen at the MD Anderson Cancer Center, key characteristics were female sex (76%), advanced age (65.9±9 years), and advanced cancer.106 Most of the events occurred in close temporal proximity to 3 types of cancer interventions: surgery, stem cell transplantation, and chemotherapy. In the latter group, 64% were able to resume different chemotherapies on cardioprotective therapies within 1 month without any recurrences.

Although the exact pathophysiology of apical ballooning syndrome is still to be defined, induction of abnormal coronary vasoreactivity is a presumed mechanism and what the aforementioned chemotherapeutic agents have most in common. In a patient who developed this syndrome with 5-FU therapy, for instance, it could be documented that 5-FU changed the normal coronary vasoresponse to acetylcholine to paradoxical vasoconstriction.35,107 The response to catecholamines might be similarly altered, and changes in vasoreactivity might extend to the coronary microcirculation, generating the substrate for abnormal perfusion and contraction.95,108,109 Furthermore, a new mechanism unraveled by chemotherapeutic agents is the inhibition of PDGF signaling, pericyte function, and survival, which influences endothelial cells and cardiac function.99,102 Injury to the endothelium and the microvasculature also underlies the all-trans retinoic acid differentiation syndrome, and cardiac stunning has been reported in patients with acute promyelocytic leukemia who are developing this syndrome with retinoic acid treatment.110

Management

The initial care of patients who have cancer with concern for apical ballooning syndrome should follow published ACS guidelines. In those with ST-segment elevation, hemodynamic instability, or persistent chest pain, emergent referral to the catheterization laboratory is to be made. If these features are absent and a high level of suspicion for apical ballooning...
syndrome is present, the combination of typical findings on echocardiography and normal coronary arteries on coronary computed tomography angiography may suffice for diagnosis and management decisions in a number of cases, especially if there are additional factors that favor a noninvasive approach. Coronary angiography and left ventriculography, however, can be safely performed, even with low platelet counts and higher bleeding risks. In patients with angiographically normal coronary arteries, structural abnormalities, even of subtle extent such as erosions, can be revealed by adjunctive invasive techniques such as optical coherence tomography. Alteration in vasoreactivity on the epicardial and microvascular level in patients with typical and atypical ACS (and non-ACS presentations alluded to above, as well) can be recognized by vasoreactivity studies with acetylcholine (endothelial function), methergine (vascular smooth muscle cell function), and adenosine (microvascular function). In some cases, these vasoactive agents might need to be combined with the cancer agent to reveal the vasofunctional abnormality. Vasodilator therapy (and drugs with vasodilator properties such as carvedilol and angiotensin-converting enzyme inhibitors) should be provided once a dynamic outflow tract obstruction is ruled out. If present, volume status should be optimized and metoprolol should be used. Although there is no consensus on the best preventive strategy for recurrent apical ballooning syndrome, a trial of therapy with β-blocker, angiotensin-converting enzyme inhibitors, and aspirin appear to be the anecdotal standard of care for the prevention of recurrence in patients who are likely to be exposed to the stressors again.

Claudication/Limb Ischemia
Ischemia of the limbs can be of different presentations and etiologies in patients with cancer. The primary presentation of limb ischemia in patients with cancer has been Raynaud’s and can be even to the degree of ischemic fingertip necrosis. The incidence can be as high as 30% and may signal systemically abnormal vasoreactivity and even myocardial infarction risk. It has been reported for bleomycin, vinca alkaloids, cisplatin, carboplatin, gemcitabine, and interferon-α. For some of these agents, eg, bleomycin, Raynaud’s can become noticeable as early as after the first dose and likely relates to a direct effect on endothelial cells. For others, eg, interferon-α, the mechanisms appear to be more complex, including vasospasm, thrombus formation, and immune-mediated vasculitis. Moreover, Raynaud’s can occur as a paraneoplastic phenomenon, even before the diagnosis of a malignancy or its recurrence.

A second, structural form of chemotherapy-induced vascular disease has been recognized with the emerging use of TKIs targeting the Bcr-Abl oncogenic fusion gene product, namely nilotinib and ponatinib. This entity has been coined peripheral arterial occlusive disease as characterized by rapidly progressive atherosclerosis, vessel occlusions, and formation of collateral circulation especially of the lower extremity circulation (Figure 3). The renal and visceral arteries can be affected and acute ischemic events in various vascular territories can evolve (even in the same patient) at an overall incidence of 2% to 25% for nilotinib and 9% to 48% for ponatinib. Importantly, these unfavorable dynamics can persist even when therapy is rapidly discontinued. Furthermore, in a number of cases, peripheral arterial occlusive disease progressed despite optimal medical therapy and preceded presentations of coronary and cerebrovascular disease including AMI and stroke. As expressed above, there is currently no proven concept of the underlying mechanisms by experimental studies with these drugs. Although considered, VEGF inhibition may not be the primary mechanism. At least, there have been many reports on peripheral arterial events with VEGF signaling pathway inhibitors. In meta-analyses, only ≈10% of all arterial ischemic events are peripheral in nature. However, plaque rupture of the superior mesenteric artery has been reported for a patient undergoing treatment with sunitinib. Even less common are acute thrombotic occlusions of the aorta and peripheral arteries with cisplatin therapy. Still, most of the existing literature would point out thrombosis and thromboembolism as the most frequent mechanisms of acute limb ischemia in patients with cancer. This includes presentation of acute limb ischemia in acute promyelocytic leukemia. Aortic tumors (intimal sarcoma) are rare but reported etiologies of limb ischemia.

Management
Because the consequences can be profound, there is merit in knowing about a predisposition to functional or structural peripheral arterial disease with cancer therapy. A thorough clinical history is key, and some patients may undergo provocation testing with cold stress, particularly if drugs such as bleomycin are considered. For nilotinib and ponatinib, although events can occur in patients without any history of cardiovascular disease or risk factor exposure, some studies have suggested higher event rates in patients with an unfavorable risk factor profile encouraging further prospective validation efforts (Figure 4). The merit of assessing nontraditional risk factors and procoagulant states in these patients is unknown. Because events can occur even in those without any risk factors, one may argue for general surveillance with serial ankle-brachial indices and Endo-PAT (Figure 2). Peripheral arterial disease monitoring might be particularly worthwhile; as for the 3 mentioned drugs, cases have been reported in which abnormalities of the peripheral vasculature preceded acute coronary and cerebrovascular events and thus may provide a window of opportunity. It is noteworthy that events can occur even while on antiplatelet and statin therapy. Nevertheless, it seems intuitive that these patients should be on best practice vascular therapy including (possibly dual) antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors, and amlodipine.

Cerebrovascular Events
Stroke and transient ischemic attack can occur in patients who have cancer with patterns and risk factors similar to noncancer patients. Although not at higher risk of hemorrhagic stroke, patients with cancer are at higher risk of thromboembolic events including those related to paradoxical embolization and indwelling catheters. Hypercoagulability may play a role in some patients but not in general. Likewise, not
factors were additional use of medications associated with bleeding and thrombocytopenia, whereas CNS tumors and metastases do not seem to increase the risk of intracranial bleeding.\textsuperscript{150,151} As outlined above, the combination of bevacizumab with 5-FU- or carboplatin-based therapies may more than double the overall incidence of arterial thromboembolic events, especially in those ≥65 years of age or with a previous arterial thromboembolic event (15.7%).\textsuperscript{31} In this analysis of combination therapies, as many as half of all acute ischemic events were strokes or transient ischemic attacks. However, the results of meta-analyses vary considerably, and some did not observe any increased relative risk of stroke with bevacizumab therapy.\textsuperscript{80} Structural vascular abnormalities such as atherosclerosis or dissections as underlying mechanisms are rarely reported.\textsuperscript{152} Similarly, although significant carotid artery disease can be noted with sorafenib, this seems to be the exception rather than the rule in patients presenting with stroke while undergoing therapy with VEGF signaling pathway TKIs.\textsuperscript{153–156}

Several cases of ischemic stroke have been reported with nilotinib. These developed even on optimal medical therapy, including Coumadin and without any identifiable substrate.\textsuperscript{129} In other cases, in addition to diffuse intracranial atherosclerosis, rapid progression (from 50% to 60% to subtotal occlusion within 1 year) of carotid artery disease was noted, becoming symptomatic in the setting of hypotension rather than complete or partial thrombotic occlusion.\textsuperscript{127} In a patient on ponatinib after treatment with nilotinib, concerns were raised for a Moyamoya disease-like process or vasculitis. However, on autopsy there was no evidence for either, and there was only a mild degree of atherosclerosis.\textsuperscript{157}

A Moyamoya disease-like process has also been implied as a potential side effect of interferon-α.\textsuperscript{158} Finally, posterior reversible encephalopathy syndrome can emerge as an acute cerebral event with headache, confusion, visual symptoms, and seizures. The characteristic finding is posterior cerebral white matter edema on neuroimaging attributable to impaired autoregulation of the cerebral vasculature. It is often noted with severe hypertension, and numerous cases have been reported for patients who have cancer undergoing drug therapy (Table), in particular, with VEGF signaling pathway inhibitors and the proteasome inhibitor bortezomib.\textsuperscript{159,160}

**Management**

Patients with cancer who have signs or symptoms of stroke should be managed based on published guidelines.\textsuperscript{161} This entails a stat head computed tomography to address the question of a hemorrhagic event or intracranial tumors (metastases). If negative, the decision on revascularization is to be made. Importantly, patients with cancer per se are not at a higher risk of intracerebral hemorrhage when undergoing thrombolytic therapy.\textsuperscript{\textit{152}} However, patients who experience a thrombotic stroke as a consequence of chemotherapy have not been rigorously studied in fibrinolysis trials. Low platelet count (<100,000) and abnormal plasma glucose (<50 or >400 mg/dL) are contraindications to lytic therapy that can be quite relevant for patients who have cancer. Further workup of underlying pathologies such as thrombotic occlusion, critical stenosis, or dissection by imaging of the cerebral vasculature...
should be pursued on an as needed basis. A 12-lead ECG should be obtained to assess for atrial fibrillation and an echocardiogram to assess for a patent foramen ovale, valve abnormalities, regional wall abnormalities, and aneurysms as potential sources of thromboembolism.165 An emergency neurology referral should be made at the onset of presentation. Care decisions (acute and long-term) are to be made in the context of the patients’ overall prognosis.

Evolving Insight Into and Concepts of Cardiovascular Diseases

New Insights Into Vascular Biology and Pathology by Cancer Therapy

One of the most stunning and puzzling observations in recent times has been the rapid progression of vascular disease and acute ischemic events noted in patients undergoing treatment with the Bcr-Abl inhibitors nilotinib and panatinib, yet these observations do provide an opportunity to identify the role of their molecular targets in vascular biology and pathology. Indeed, recent studies on the vascular role of Abl kinase have provided unprecedented insight. Loss of Abl expression confined to the endothelial cells impaired endothelial cell viability, loss of vasculature, tissue necrosis/apoptosis, and fetal lethality. Animals that survived into adulthood had normal gross vascular morphology but still developed major organ abnormalities later in life. Cardiomegaly was evident and areas of infarction that were devoid of blood vessels despite a generally preserved capillary density. Loss of vascular density was noted in the lungs along with an abundance of hemosiderin-laden macrophages and fibrin deposition in keeping with defective pulmonary vascular integrity, pulmonary hemorrhage, and interstitial fibrosis. The presence of marked left atrial dilatation has supported the speculation that increases in left ventricular filling pressures contributed to these abnormalities and cor pulmonale. The presence of thrombi in lung microvessels along with swelling of the endothelium may further indicate endothelial injury. Therefore, loss of functional Abl may not only impair the formation of new vessels but the function and stability of existing vessels as a result of endothelial cell damage. In agreement, it was subsequently discovered that endothelial Abl kinases are of crucial significance for Tie2 receptor signaling and angiopoietin 1–mediated endothelial cell survival and are themselves activated by this pathway in a positive feedback loop. VEGF stimulates Abl as well, and Abl seems to be involved in the prosurvival effects of VEGF on endothelial cells, especially under stress conditions such as serum starvation. Abl inhibition may therefore be even more important under conditions that negatively impact endothelial function.164 Furthermore, Abl mediates the increase in endothelial permeability induced by VEGF (via VEGF-R2) and histamine and thrombin (via G-protein–couples receptors).165 This has been attributed to an inhibitory action of Abl on the endothelial barrier-promoting GTPases Rac1 and Rap1, which promote cortical actin remodeling and adherens junction stability. Accordingly, Abl inhibition with imatinib improved endothelial barrier function by enhancing Rac1 activity and enforcing adhesion of endothelial cells to the extracellular matrix.165,166 Furthermore, imatinib improves endothelial apoptosis induced by inhibition of integrins and F-actin polymerization.167 Alternations of integrins and F-actin–related signaling has been implicated in diabetic vasculopathy, and it might be for this reason that imatinib was shown to prevent the development of atherosclerosis in a rodent diabetes model. Interference with the stimulation of platelet-derived growth factor-B signaling might have an additional contributing role in this model, and in animals without diabetes mellitus, as well.168,169 Imatinib also inhibits Kit, colony-stimulating factor 1 receptor, and discoidin domain receptors, but there is no indication based on the available literature that inhibition of any of these could have a contributing role. Dissecting the differences between the different Bcr-Abl inhibitors is crucial in view of the spectrum of activities and side effects (Figure III in the online-only Data Supplement). Thus far, there are no experimental in vivo studies that delineate the vascular consequences of the modulation of any of these pathways.

Targeted therapies have also brought to stage a cell type not much thought of in the coronary circulation: the pericyte (Figure 5). A unique observation, indeed, is the rarefaction of microvascular pericytes without a change in the capillary density in the myocardium of mice treated with sunitinib. Importantly, these mice developed microvascular dysfunction with impairment in coronary flow reserve. They also developed reduced contractile function and contractile reserve.170–172 In experiments aiming to restore pericyte function and survival, this sequence could be reversed, indicating causality. Finally, observations could be reproduced by a PDGF receptor inhibitor, defining the molecular pathway. Unexpectedly thereby, new insight was gained into the mechanisms of coronary microvascular dysfunction and the significance of pericycle-endothelial cell coupling for microvascular integrity. As outlined in Figure 6, endothelial cells produce PDGF to maintain the survival of pericytes, which produce VEGF and angiopoietin-1 to maintain the function of endothelial cells, further reinforced by Abl.

Proteasome inhibitors are another example of drugs used in cancer therapy that facilitated the discovery of new aspects of atherosclerosis, namely protein quality disease aspects.173 The proteasome is the main protein degradation system in eukaryotic cells and essential for protein processing, and the removal of proteins that are damaged or misfolded to a degree that is beyond repair, as well.174 Accumulation of these dysfunctional proteins (as a consequence of proteasome inhibition) is toxic for the cell, linked to endoplasmic reticulum stress, and the so-called unfolded protein response, all nontraditional avenues in the understanding of the pathophysiology of atherosclerosis.175 Taken together, born out of studies on the cardiovascular side effects of target therapies, important new insight into vascular biology, pathology, and pathology has been gained.

Vascular Side of Cardiac Toxicity With Cancer Therapy

The observation that patients on vascular-directed cancer therapies such as bevacizumab develop cardiomyopathy and heart failure leads to the question whether this is a reflection of a direct impact of VEGF on cardiomyocytes or an indirect impact of VEGF on myocardial function via endothelial cells
and the coronary microvasculature. Initial studies indicated that cardiomyocytes are the major source of VEGF in the heart and, in a paracrine manner, remain essential for the coronary microvasculature. Indeed, mice with cardiomyocyte-specific deletion of VEGF developed, in conjunction with reduced myocardial vascularization, dilated cardiomyopathy with wall thinning and evidence of a significantly blunted contractile response to dobutamine. Conditional and reversible suppression experiments furthermore indicated that myocardial VEGF is a critical element to match microvascular density to myocardial demand and perfusion to contraction. Accordingly, VEGF blockade can lead to reversible cardiac dysfunction secondary to hypoperfusion, a state reminiscent to hibernation. Intact autocrine VEGF signaling on the level of endothelial cells, however, remains a condition sine qua non. For mice with deletion of VEGF confined to the endothelial lineage (but preserved in cardiomyocytes) had a lower vascular density in the heart and developed a dilated cardiomyopathy without wall thinning despite evidence of microinfarctions. These infarctions related to the apoptotic

Figure 5. Illustration of the pericyte structure within the capillary microcirculation of the heart.

Figure 6. Schematic presentation of pericyte-endothelial-myocardial interaction. AC indicates adenylate cyclase; Ang-1, angiopoietin 1; IP, prostacyclin receptor; M2, muscarinic receptor; NO, nitric oxide; NOS, NO synthase; NRG-1, neuregulin-1; sGC, soluble guanylyl cyclase; PDGR, platelet-derived growth factor; PDGFR, PDGFR receptor; VEGF, vascular endothelial growth factor; and VEGFR, VEGF receptor.
loss of endothelial cells, platelet activation and aggregation, and the formation of intravascular thrombi, and accounted for sudden cardiac death in 20- to 25-week-old mice. These studies clearly outlined that endothelial VEGF is required for the stability of the vasculature and organ function. In vitro studies suggested further that this becomes even more important under stress conditions such as hypoxia, and paracrine sources of VEGF cannot compensate for any impairment in autocrine VEGF signaling (as accomplished by TKIs), so vital for endothelial cell survival. Intriguingly, in an animal model of diabetic cardiomyopathy, downregulation of VEGF expression was identified as the sentinel event that preceded endothelial cells apoptosis, a decline in capillary density and myocardial perfusion and the subsequent sequence of cardiomyocyte death, fibrosis, and diastolic and finally systolic myocardial perfusion and the subsequent sequence of capillary endothelial cells apoptosis, a decline in capillary density and myocardial perfusion and the subsequent sequence of cardiomyocyte death, fibrosis, and diastolic and finally systolic dysfunction. Importantly, this sequence could be reversed by VEGF repletion. Peripartum cardiomyopathy may share some of these aspects, because the release of VEGF inhibitors, such as soluble FMs-like tyrosine kinase 1 by the placenta in the late stages of pregnancy, seemingly induces endothelial cell dysfunction and apoptosis followed by cardiomyocyte dysfunction. Secretion of soluble FMs-like tyrosine kinase 1 is also significantly elevated in preeclampsia, suggesting overlapping cardiotoxic pathophysiology. Thus, various lines of evidence point out the significance of an intact VEGF signaling system for normal cardiac function. Interference with this system can induce cardiomyopathy or cardiotoxicity in the case of chemotherapeutic agents.

The outlined vascular capacity of the heart is modulated further by signaling pathways that have become additional targets of chemotherapeutic agents. In fact, their role has been recognized in the pursuit of defining the cardiotoxicity of receptor TKIs, particularly those that inhibit, not only the VEGF receptor, but also the PDGF receptor. One of the key observations was the recognition of the PDGF receptor β (PDGFRβ) as an essential regulator of the angiogenic program in response to hypoxia, and afterload stress, as well. Mice with inducible, cardiac-specific PDGFRβ deficiency did not mount an increase in microvascular density, so crucial as an adaptive mechanism for cardiac hypertrophy in response to increased afterload. This coincided with a decrease in myocardial perfusion and a reduction in coronary flow reserve. Myocardial hypoxia and fibrosis were evident on histology. In addition to alteration in the angiogenic profile, there was evidence of impairment in the activation of cardioprotective stress response pathways, and ventricular dilation, cardiomyopathy, and heart failure would evolve in mice with PDGFRβ deficiency subjected to afterload stress. PDGFRβ, however, was not found to be essential for normal cardiac function or baseline cardiac function (in the absence of any stressor). Accordingly, patients with hypertension and myocardial ischemia might be higher risk with drugs that inhibit PDGFRβ signaling such as sunitinib and sorafenib, and, intriguingly, this matches clinical observation. However, because these patients are also at risk of developing cardiomyopathy with bevacizumab, the significance of VEGF signaling has to be taken into account. In addition, it might be the interplay of the increase in afterload with VEGF inhibition that generates a higher risk of cardiotoxicity with sunitinib and sorafenib than with other PDGFR inhibitors that lack VEGF receptor inhibition and have a lower risk of cardiotoxicity (eg, imatinib).

Extending these observations, additional experimental studies provided a completely novel aspect to cancer therapy–induced cardiotoxicity and microvascular and cardiac dysfunction, in general, for it was realized that sunitinib could indeed recapitulate the observation made in PDGFRβ-deficient mice. Importantly, the loss of pericytes preceded the reduction in coronary flow reserve and cardiac function, and these consequences were prevented by strategies of pericyte protection, eg, concomitant thalidomide treatment. These observations are revolutionary because, for the first time, they point out the pivotal role of pericytes for the coronary microvasculature and a sequence that starts with pericyte dysfunction, generates microvascular dysfunction, and culminates in cardiac dysfunction. Cross talk on the level of the coronary microcirculation extends to pericytes, endothelial cells, and cardiomyocytes and might be of relevance for various forms of cardiomyopathy (Figure 6).

These new observations may also modify the concept of endothelial-myocardial coupling as it evolved based on studies on the mechanisms of trastuzumab-induced cardiotoxicity. According to prevailing theory, trastuzumab interferes with human endothelial growth factor receptor (HER) dimerization impacting various cardiomyocyte signaling pathways, especially those of significance for stress responses. The endothelial link is provided in the fact that the natural ligand to accomplish HER dimerization is neuregulin-1, which is produced by the endothelial cells of the microvasculature. One may argue that dysfunctional endothelial cells have less of a reserve to produce neuregulin-1 and thus bestow a reduced reserve of the myocardium to any stressors. Indeed, an inverse correlation was noted between circulating levels of neuregulin-1 and extent of coronary artery disease. Moreover, depressed NRG-1 synthesis impairs cardiac recovery after an ischemic insult, and impairment in NRG-1/HER signaling was found in experimental diabetic cardiomyopathy. Intriguingly, patients with coronary artery disease and those with diabetes mellitus are also at increased risk of anthracycline-induced cardiotoxicity, and provision of neuregulin improves cardiac function after anthracycline-induced myocardial injury. Thus, there might be an element of neuregulin-related endothelial-myocardial coupling even in mechanisms of injury of classic cardiotoxic drugs such as anthracyclines. Along these lines, one would have to postulate that patients are the more susceptible to trastuzumab cardiotoxicity the greater the activity/stimulation of the NRG-1/HER signaling pathway. This would explain the high incidence of cardiomyopathy when trastuzumab is given in close temporal proximity to anthracyclines. However, it does not explain why patients with concomitant cardiovascular risk factors or disease are at higher risk unless this pathway is very crucial and any further reduction from baseline is detrimental. Experimental studies have outlined that HER2 deficiency leads to the development of dilated cardiomyopathy, preserved contractile response to dobutamine, but impaired adaptation response to afterload increase. Thus far, no studies have assessed any correlation with the microvascular density and response.
Summary and Conclusions
Similar to the recognition of cardiotoxicities with cancer therapeutics, vascular toxicities have been noted for 4 decades, but it was not until the introduction of targeted therapies that they received greater attention. The new era of cancer therapy has introduced a broad spectrum of cardiovascular toxicities that the practicing cardiologist will be increasingly confronted with and should be knowledgeable of. In addition, these new therapies have provided novel insights into cardiovascular diseases, pathomechanisms, and paradigms, which is of great interest to the cardiovascular research community. Vascular toxicity with cancer therapy: the old and the new, an evolving avenue.

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Vascular Toxicities of Cancer Therapies: The Old and the New – An Evolving Avenue
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SUPPLEMENTAL MATERIAL

Supplemental Tables 1-3

Supplemental Figures 1-3
### Incidence (%) and risk (odds ratio, OR) of systemic hypertension* with VEGF signaling pathway inhibitors based on meta-analyses, most recently published by June 2015

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* Hypertension grades per National Cancer Institute's Common Terminology Criteria for Adverse Events (see Supplemental Table 2), high grade represents grade 3 or higher
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<td>Requiring therapy or more intensive therapy than previously</td>
<td>Requiring more than one drug or more intensive therapy than previously</td>
<td>Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg); more than one drug or more intensive therapy than previously used indicated</td>
</tr>
<tr>
<td>4</td>
<td>Hypertensive crisis</td>
<td>Hypertensive crisis</td>
<td>Life-threatening consequences (e.g., hypertensive crisis)</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention needed</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>Death</td>
<td>Death</td>
<td>Death</td>
</tr>
</tbody>
</table>
## Management of 5-FU/Capecitabine cardiotoxicity

<table>
<thead>
<tr>
<th>At the time of acute presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stop administration of the drug</td>
</tr>
<tr>
<td>• Use nitrates or calcium channel blockers (CCB)</td>
</tr>
<tr>
<td>• Cardiac monitoring, CCU for pts with cardiac biomarker elevation &gt;2x upper limit of normal for ≥ 72 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At the time of consideration of re-challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 3-day course of nitrates or CCB, 24 hours before, during, and after re-challenge</td>
</tr>
<tr>
<td>• Continuous ECG monitoring on the day of drug administration</td>
</tr>
<tr>
<td>• Avoid in patients with myocardial infarction as a prior complication of therapy</td>
</tr>
</tbody>
</table>
Supplemental Figure legends

**Supplemental Figure 1.** Illustration of pre-therapy evaluation of patients who are to undergo treatment with chemotherapeutics with high hypertension risk.

**Supplemental Figure 2.** Illustration of on-therapy evaluation of patients who are to undergo treatment with chemotherapeutics with high hypertension risk.

**Supplemental Figure 3.** Illustration of ST-segment elevation acute coronary syndrome with 5-FU therapy.
Supplemental Figure 1

**Hypertension**

- Risk factors for hypertension and events:
  - Uncontrolled BP
  - Organ damage, e.g. LVH
  - Established CVD
  - CKD ≥ Stage 3
  - Diabetes mellitus
  - ≥ 3 CV risk factors
  - Obesity
  - Age ≥ 60-65

**Cancer**

- Cancer therapy options
  - High hypertension risk: VEGF inhibitors, mTOR inhibitors, Ponatinib, Cisplatin

**Risk/benefit assessment**

- Therapy initiation or intensification (towards goal of <140/90 mmHg prior to start of cancer therapy)

- Prohibitive risk
  - Poorly controlled angina
  - ACS within 6 months
  - Uncontrolled heart failure
  - Uncontrolled blood pressure
  - Uncontrolled arrhythmia
  - Significant QTc prolongation

- Treatment with close follow-up

- Repeat assessment
Supplemental Figure 2

Oncology patient

Cancer therapy with high hypertension risk:
VEGF inhibitors, mTOR inhibitors, Ponatinib, Cisplatin

Blood pressure (BP) assessment weekly with first cycle, then every 2-3 weeks

Therapy initiation or intensification (towards BP goal of <140/90 mmHg)
Temporary hold or dose reduction if BP >180/110 mmHg or shock
Supplemental Figure 3

Baseline

5-FU infusion

Chest pain

Nitroglycerin

Chest pain resolution