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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 “off-target” effects. The latest examples are tyrosine kinase inhibitors targeting the Philadelphia Chromosome mutation product, which have been associated with progressive atherosclerosis and acute vascular events. Additionally, 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 cardiotoxicity of 5-Fluorouracil and may be the underlying the mechanism of presentation of apical ballooning syndrome with various chemotherapeutics. Classical chemotherapeutics such as cisplatin, often used in combination with bleomycin and vinca alkaloids, can lead to vascular

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events including acute coronary thrombosis, 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 it pertains to clinical practice as well as the conceptualization of cardiovascular diseases. Vascular toxicity with cancer therapy: the old and the new, an evolving avenue.

Keywords

cardiovascular complications; drug therapy; vasospasm; endothelial dysfunction; angina pectoris; chemotherapy

"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 cancer patients has received increasing attention, and demands in this area have and will continue to grow considerably. While the mechanisms, monitoring, and management of cardiotoxicities have received broad attention, vascular toxicities remain under-recognized. 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 shot-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 as well as vascular toxicity aspects of classical cardiotoxic drugs ("chemo-vaso-cardio interaction").

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 chemotherapeutics (**Table 1**) 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 20-30% higher than expected and an overall rate of systemic hypertension as high as 70%.[2] Intensification of therapy (hypertension grade 3, see **Supplemental Table 1**) was, however, required only in 10-20% of patients and life-threatening hypertensive crises were rare (approximately 1%). As pointed out in meta-analyses (**Supplemental Table 2**), 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 renal cell carcinoma patients) and certain ethnic populations (e.g. in Japanese patients in axitinib trials: 84% overall incidence of hypertension, 70% high grade).[5] The primary at risks groups, however, are those with pre-existing hypertension, advanced age (≥ 60 to 65 years), history of smoking, hypercholesterolemia, or obesity (Supplemental Figure 1).[6, 7] Increases

in blood pressure can occur within hours of therapy initiation, especially with tyrosine kinase inhibitors (TKIs), are most pronounced during the first few cycles of therapy, and range in the order of 10 to 20 mmHg systolic and 5 to 15 mmHg diastolic.[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 rarefication, 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 (eNOS), with NO being crucial for normal endothelial function, vascular homeostasis and angiogenesis.[8] Activation of the endogenous endothelin system might an additional contributing factor, whereas clinical studies have not confirmed a role for the renin-angiotensin system.

Mammalian target of rapamycin (mTOR) inhibitors are an other class of chemotherapeutics that have been associated with hypertension. The risk is higher with everolimus (overall 4-30%, hypertensive crisis 1%) than temsiolimus (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 cardio-metabolic profile.[9]

Management

It is recommendable that patients considered for therapy with agents with known hypertension risk undergo a thorough evaluation of their baseline status (Supplemental Figure 1). 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 (Supplemental Figure 2).[10] No clinical trial data are available to guide recommendations of anti-hypertensive therapies in cancer patients and thus the JNCVIII 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 are more effective but non-dihydropyridines should be avoided as 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 cancer patients encompasses a broad differential and can be provoked by cancer therapies. Dasatinib, a TKI of BCL-ABL, used in patients with Philadelphia Chromosome-positive (Ph+) leukemias, is the most intriguing example of a chemotherapeutic that can induce pre-capillary pulmonary hypertension. Increases in pulmonary arterial pressures (average mean pulmonary pressure 46 mmHg, average right ventricular systolic pressure 65 mmHg) can occur in up to 11% of patients on dasatanib.[12, 13] Importantly, while improving upon cessation of therapy, dasatinib-induced pulmonary hypertension may not be fully reversible. In the original series of nine patients, pulmonary hypertension treatment was initiated in three with continuation of endothelin receptor antagonists in two 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 intra-pulmonary 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 tyrosine kinase inhibitors, VEGF signaling pathway directed or not, are associated with pulmonary hypertension, probably due to remarkable differences in the molecular targets. Dasatinib yields the best in vitro and in vivo results with regards to the treatment of pulmonary hypertension due to the concomitant inhibition of 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.[12] On the contrary, imatinib, inferior in experimental studies, improves pulmonary hypertension and exercise tolerance in clinical practice.[18] The definite mechanisms of dasatinib-induced pulmonary hypertension remain unknown, but its association with exudative pleural effusions, pericardial effusion and lymphocytic accumulations in pleural and bronchoalveolar lavage and biopsies point towards a potential immune mechanisms.[19]

Another chemotherapeutic notoriously associated with pulmonary hypertension is bleomycin. The overall risk is approximately 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 (IFN) alpha can induce pulmonary vasculitis and pulmonary hypertension for unknown reasons.[29] Immune mechanisms are discussed among others, similar to the discussion on the effects of IFN alpha on the peripheral arterial vasculature. While not necessarily vascular in nature, it should not be left unmentioned that mTOR inhibitors can induce a non-infectious pneumonitis.[30]

Management

It is recommendable that all patients undergo evaluation for signs and symptoms of underlying cardiopulmonary disease prior to 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 immediate re-evaluation, which should include an electrocardiogram, 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 cancer patients 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 1-18% of patients exposed, and its oral pro-drug capecitabine at a 50% lower rate. The onset can be rather quickly (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 non-invasive 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 chemotherapeutics known to induce similar types of chest pain are the taxanes, namely paclitaxel at an incidence of 0.2-4%.[36-38] Similar to 5-FU, vasoconstriction (spasm) has been considered to be key mechanism. In distinction though, cardiac rhythm disturbances are more common with taxanes.[36]

Cisplatin, even more so in combination with bleomycin and/or vinca alkaloids, can provoke chest pain presentations at an incidence as high as 40%.[3940, 4142 .43, 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]

Vascular endothelial growth factor (VEGF) signaling pathway inhibitors are another class of drugs well known to be associated with angina at an incidence or 1-15%. Again, endothelial dysfunction likely plays an important role, as inhibition of VEGF receptor signaling impairs stimulation of endothelial NO synthase (eNOS) activity via the Akt/PKB pathway.[46] Moreover, eNOS uncoupling may occur with an increase in oxidative stress, activation of the endothelin system, furthering the propensity towards 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 sub-occlusion of the left main over the course of only 4 years.[54] These dynamics are confirmed by experimental studies with a pan-VEGF receptor inhibitor.[48] On the other hand, bevacizumab reduced neovascularization and growth of established plaques similar to other anti-angiogenesis inhibitors in experimental models.[55] Thus, VEGF signaling pathways 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, cancer patients can also develop signs and symptoms of myocardial ischemia as a consequence of coronary artery compression by various cardiac and non-

cardiac tumors.[56] Malignant tumors, even from the left atrium, can cause coronary compression which may lead to myocardial infarction.[57] As another example, the left main stem can be involved in the setting of mediastinal tumors such as lymphoma.[58] Right ventricular grove with encasement but without compression of the right coronary artery has been described with mediastinal diffuse large B-cell lymphoma and thymoma, which has been coined the “floating artery sign”.[59] 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 cancer patients at risk for the outlined side effects. The Society of Cardiac Angiography and Intervention (SCAI), however, recently commissioned a consensus effort in this area (Figure 2). [60] Assessment of baseline cardiovascular history and risk is the key first step, and any potentially modifiable risk factor and disease state should be optimized prior to 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 I chemotherapy-related vasotoxicity, e.g. 5-FU) and those with a potentially long-term and structural risk (type II chemotherapy-related vasotoxicity, e.g. nilotinib and ponatinib). [61] The goals, modes, and duration of testing vary accordingly. They are to be more functionally directed before and during therapy for type I agents, e.g. peripheral vasoreactivity testing by Endo-PAT, whereas they are to include structural assessments and their consequences for type II agents, e.g. coronary angiogram and cardiac stress tests. While 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 I agents, administration of nitroglycerin and/or calcium channel blockers is the best initial diagnostic and therapeutic step (Supplemental Figure 3). Subsequently, the decision is to be made on further testing for structural heart disease. 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 usually recommendable if further treatment with the same or a similar drug is considered and the patient is expected to derive a significant oncology benefit from it. Under those circumstances, the goal is to facilitate continuation of chemotherapy while managing, mitigating cardiovascular disease risk and side effects. Moreover, a more comprehensive imaging evaluation is recommendable 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/or reduction in chemotherapy dosing in general.[39, 62] Pre-treatment with nitrates and/or calcium channel blockers prior to exposure to type I agents is another option. As the underlying mechanisms of vascular toxicity with type II agents remain to be elucidated, no definite management recommendation can be given. Dual antiplatelet therapy, statins, ACE inhibitor, and amlodidpine have been elected in selected cases.[63]

Acute coronary syndromes (ACS)

ACS can develop in cancer patients encompassing the entire spectrum from unstable angina to acute myocardial infarction (AMI) and even sudden cardiac death. As outlined above, a number of chemotherapeutics 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 capecitabine (Supplemental Figure 3).[64-66] Profound and prolonged vasospasm has also been implied in ACS presentations of paclitaxel, gemcitabine, rituximab, and sorafenib.[37, 38, 51, 67-69] Other type II ACS (MI) scenarios can be induced by tachycardia, hypotension, hypoxia, and anemia in cancer patients with significantly reduced myocardial reserve due to coronary artery disease or potentially patho-anatomical variants such as myocardial bridging.

Type I ACS (MI) scenarios are also encountered as a consequence of the well-established types of plaque complications. Given the toxic effect of chemotherapeutics on the endothelial cells, there might be a greater propensity towards erosion in cancer patients. A classic example is cisplatin, with and without bleomycin and/or vinca alkaloids. Single and even multi-vessel coronary thrombosis can be evident on angiography without any underlying atherosclerosis.[70-73].[74-76] Erosion as the leading mechanism is supported by experimental studies pointing out the induction of endothelial damage to the point of apoptosis and stimulation of thromboxane production, platelet activation, and platelet aggregation.[70, 72, 77, 78] Accordingly, these acute coronary events can occur in any cancer patients without prediction. Furthermore, cisplatin levels can remain detectable for years after therapy and so can the risk for chest pain episodes and acute ischemic events. [79]

The significance of the VEGF signaling cascade for endothelial cell function and survival might account for the ischemic event risk encountered with inhibitors of this pathway. Fatal AMI is rare (<0.1%) but ACS occurs in 2% of patients treated with bevacizumab, a more than 2-fold higher relative risk than in controls.[80] This risk, however, seems to be modified by additional patient and treatment-related factors. For instance, the addition of bevacizumab to 5-FU- or carboplatin-based therapies more than doubles the overall incidence of arterial thromboembolic events (from 1.7% to 3.8%, 40% of these cardiac) and the risk seems to be particularly high in those age 65 or older (7.1% incidence) or with a prior arterial thromboembolic event (15.7%).[81] The overall relative risk of arterial thrombotic events with bevacizumab is 1.5 and two times higher with VEGF receptor TKIs, with the highest relative risks being observed with sunitinib, pazopanib, and sorafenib (5.9, 4.6, and 2.3, respectively).{Qi, 2014 #631} While plaque rupture has been reported for patients undergoing treatment with sunitinib in other vascular territories, such events have not been reported for the coronary circulation.[54, 82] In fact, in the initial retrospective series, nearly 10% of patients treated with sunitinib or sorafenib developed an acute cardiac event with cardiac biomarker elevation and regional wall motion abnormalities but coronary angiography remained unremarkable.[83] Moreover, in experimental studies VEGF inhibitor therapy did not predispose to a vulnerable phenotype.[4855] For this reason, only vascular disrupting agents may be potent enough to disintegrate the fragile plaque neovessels leading to plaque hemorrhage.[84] An additional predisposing factor to acute vascular events with

VEGF inhibitors, however, might be their impact on platelet function. Similar to PF4, which plays a pathomechanistic role in heparin-induced thrombocytopenidia, VEGF binds heparin and in immune complexes with bevacizumab can bind to FCyRIIa (CD32) inducing aggregation and pro-coagulant activity.[85]

Whether there is any mechanistic overlap with ACS in patients on 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.[86, 87] In the few detailed cases 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).[63, 88] In one of the larger retrospective series on nilotinib, ACS presentations were encountered in 7.5% of the patients, occurring at any point in time during and even a month after treatment.[89] Two of the six patients had an AMI, one with a fatal outcome, and three of the other four patients experienced recurrent events, two of which had undergone percutaneous coronary intervention (PCI).[89]

Given a predisposition to a pro-coagulant state in general, cancer patients are 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.[90, 91] Last but not least, other atypical mechanisms of acute coronary syndrome are to be entertained in cancer patients including spontaneous coronary artery dissection.[92-94] Extrinsic compression by a tumor mass is usual a gradual phenomenon but sudden growth could lead to unstable and acute presentations.

Management

Patients who developed 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 cancer patients despite anemia and coagulation abnormalities. Further management decisions are to be guided based on the findings. If uncertainty remains with regards to underlying coronary artery disease and arterial pathology, intravascular ultrasound (IVUS) and/or optical coherence tomography (OCT) might be useful. The decision on PCI 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 or older and a prior history of an arterial thrombotic event (12.5% versus 22.9%), however, 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, cancer patients can present with apical ballooning syndrome, precipitated by various factors.[95] In fact, this entity might be relatively more common among cancer patients given the exposure to various and significant stressors.

Moreover, this syndrome has been noted with the use of a number of chemotherapeutics, including 5-FU, capecitabine, cytarabine, axitinib, sunitinib, bevacizumab, rituximab, trastuzumab, and combretastatin.[96-105] In a series of 38 cancer patients with stress cardiomyopathy from the MD Anderson medical center, key characteristics were female gender (76%), advanced age (65.9±9 years), and advanced cancer.[106] Most of the events occurred in close temporal proximity to three 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 one month without any recurrence.

While 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 chemotherapeutics have most in common. In a patient who developed this syndrome with 5-FU therapy, for instance, it could be documented that 5-FU altered the at baseline normal coronary vasoresponse to acetylcholine to paradoxical vasoconstriction.[10735] 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 mechanisms unraveled by chemotherapeutics 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 ATRA 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 cancer patients 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, which favor a non-invasive 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 OCT and IVUS. Alteration in vasoreactivity on epicardial and microvascular level in patients with typical and atypical ACS (as well as non-ACS presentations alluded to above) 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.[107] Vasodilator therapy (and drug with vasodilator properties such as carvediolol and ACE inhibitors) should be provided once a dynamic outflow tract obstruction is ruled out. If present, adequate volume status and metoprolol should be used.

While there is no consensus on the best preventive strategy for recurrent apical ballooning syndrome, a trial of long-term therapy beta-blocker, angiotensin converting enzyme inhibitors and aspirin appear to be the “anecdotal standard of care” for prevention of recurrence in patients who are likely to be exposed to the stressors again.[111]

Claudication/ limb ischemia

Ischemia of the limbs can be of different presentations and etiologies in cancer patients. The primary presentation of limb ischemia in cancer patients 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.[43, 44] It has been reported for bleomycin, vinca alkaloids, cisplatin, carboplatin, gemcitabine, and IFN alpha.[29, 112-115] For some of these agents, e.g. bleomycin, Raynaud’s can be noticeable as early as after the first dose and likely relates to a direct effect on endothelial cells.[116] For others, e.g. IFN-alpha, the mechanisms appear to be more complex including vasospasm, thrombus formation and immune-mediated vasculitis.[117] Moreover, Raynaud’s can occur as a paraneoplastic phenomenon, even before the diagnosis of a malignancy or its recurrence.[118]

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.[87, 119] This entity has been coined peripheral arterial occlusive disease (PAOD) 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 2-25% for nilotinib and 9-48% for ponatinib.[120-122123-125] Importantly, these unfavorable dynamics can persist even when therapy is rapidly discontinued.[126-128] Furthermore, in a number of cases PAOD progressed despite optimal medical therapy and preceded presentations of coronary and cerebrovascular disease including AMI and stroke.[127, 129] As expressed above, there is currently no proven concept of the underlying mechanisms by experimental studies with these drugs.

While considered, VEGF inhibition may not be the primary mechanism. At least, there have not been many reports on peripheral arterial events with VEGF signaling pathway inhibitors. In meta-analyses, only approximately 10% of all arterial ischemic events are peripheral in nature.[80] However, plaque rupture of the superior mesenteric artery has been reported for a patient undergoing treatment with sunitinib.[54, 82] Even less common are acute thrombotic occlusions of the aorta and peripheral arteries with cisplatin therapy.[130, 131] 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.[132] This includes presentation of acute limb ischemia in acute promyelocytic leukemia.[133] Aortic tumors (intimal sarcoma) are rare but reported etiologies of limb ischemia.[134]

Management

As 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, while 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).[135] The merit of assessing nontraditional risk factors and pro-coagulant states in these patients is unknown. As events can occur even in those without any risk factors, one may argue for general surveillance with serial ankle-brachial indices and/or Endo-PAT (Figure 2). Peripheral arterial disease monitoring might be particular worthwhile as for the three 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 of note that events can occur even while on anti-platelet and statin therapy. Nevertheless, it seems intuitive that these patients should be on the best practice vascular therapy including (possibly dual) antiplatelet therapy, statins, ACE inhibitor, and amlodidpine.[63]

Cerebrovascular events

Stroke and TIA can occur in cancer patients with patterns and risk factors similar to non-cancer patients. While not at higher risk of hemorrhagic stroke, cancer patients are at higher risk of thromboembolic events including those related to paradoxical embolization and indwelling catheters. [136137138] Hypercoagulability may play a role in some patients but not in general.[139] Likewise, not all but some chemotherapeutics, e.g. 5-FU and cisplatin, have been associated with a risk of stroke.[140-144] Cisplatin seems to be of particular concern and induction of endothelial cell death may generate not only local but possibly even systemic vulnerability by the production of pro-coagulant microparticles.[145] This may explain why in some cases no cause of ischemic stroke can be identified while in other cases local cranial artery thromboses can occur to the point of acute complete occlusions.[146]

Given the outlined side effect profile of arterial thrombosis, bleeding, and hypertension, concerns for stroke risk have been raised for VEGF signaling pathway inhibitors.[147] In phase I and II trials of VEGF signaling pathway inhibitors, ischemic stroke and intracranial hemorrhage occurred at a rate of 1.9% each with bevacizumab and in 0 and 3.8% of patients receiving VEGF receptor TKIs, respectively.[148] Intracranial hemorrhages occurred earlier (median of 2.6 months), often in the setting of tumor progression, and with dismal further survival. Ischemic strokes, on the contrary, were associated with prolonged therapy (median of 16.2 months) and survival. A retrospective review of the FDA MedWatch database of adverse events indicated that cranial bleeds accounted for 12.9% of all bleeding events with bevacizumab (which were 6.8% of all adverse events) and were fatal in half of the cases.[149] The greatest risk 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.[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 age 65 or older or with a prior arterial thromboembolic event (15.7%).[81] In this analysis of combination therapies, as many as half of all acute ischemic events were stroke or TIAs. However, the results of meta-analysis vary considerably and some did not observe any increased relative risk of stroke with bevacizumab therapy.[80] Structural vascular abnormalities such as atherosclerosis or dissections as underlying mechanisms are rarely reported.[152] Similarly, while 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 VEGF signaling pathway TKIs. [153-156]

Several cases of ischemic stroke have been reported with Nilotinib. These developed even on optimal medial therapy including Coumadin and without any identifiable substrate.[129] In other cases, in addition to diffuse intracranial atherosclerosis, rapid progression (from 50-60% to subtotal occlusion within one year) of carotid artery disease was noted, becoming symptomatic in the setting of hypotension rather than complete or partial thrombotic occlusion.[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 the degree of atherosclerosis was only mild.[157]

A MoyaMoya disease-like process has also been implied as a potential side effect of interferon-alpha.[158] Finally, posterior reversible encephalopathy syndrome (PRES) 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 due to impaired autoregulation of the cerebral vasculature. It is often noted with severe hypertension and numerous cases have been reported for cancer patients undergoing treatment with a number of drugs listed in **Table 1**, particularly VEGF signaling pathway inhibitors and the proteasome inhibitor bortezomib.[159160]

Management

Cancer patients with signs or symptoms of stroke should be managed based on published guidelines.[161] This entails a stat head CT to address the question of a hemorrhagic event or intracranial tumors (metastases). If negative, the decision on revascularization is to be made. Importantly, cancer patients per se are not at a higher risk of intracerebral hemorrhage when undergoing thrombolytic therapy.[162] However, patients who suffer 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 cancer patients. Further work-up 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.[163] 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 panotinib. These observations yet 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. Confined to the endothelial cells, loss of *Abl* expression impairs endothelial cell viability, loss of vasculature, tissue necrosis/apoptosis and fetal lethality. Animals that survived into adulthood have normal gross vascular morphology but still developed major organ abnormalities later in life. Cardiomegaly was evident with 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 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 dilation 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 angiopoetin 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 pro-survival effects of VEGF on endothelial cells, especially under stress conditions such as serum starvation. Abl inhibition may therefore be even more so 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 as well as in animals without diabetes.[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 (Supplemental Figure 3). 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 rarefication 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 PDGFR inhibitor, defining the molecular pathway. Unexpectedly thereby, new insight was gained into the mechanisms of coronary microvascular dysfunction and the significance of pericyte-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 as well as the removal of proteins that are damaged or misfolded to a degree that is beyond repair.[174] Accumulation of these dysfunctional proteins (as a consequence of proteasome inhibition) is toxic for the cell, links to endoplasmatic reticulum stress and the so-called unfolded protein response, all non-traditional 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, physiology, and pathology has been gained.

The “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.[176] 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.[176] Sequestration experiments furthermore indicated that myocardial VEGF is a critical element to match microvascular density to myocardial demand and perfusion to contraction.[177] Accordingly, VEGF deploy can lead to reversible cardiac dysfunction stages secondary to hypoperfusion, a state reminiscent to hibernation. Intact autocrine VEGF signaling on the level of endothelial cells, however, remains key for these paracrine actions of VEGF.[178] 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 loss of endothelial cells, platelet activation and aggregation and the formation of intravascular thrombi and accounted for sudden cardiac death in 20 to 25 weeks old mice.[178] 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.[178] 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, diastolic and finally systolic dysfunction.[179] Importantly, this sequence could be reversed by VEGF repletion.[179] Peripartum cardiomyopathy may share some of these aspects as the release of VEGF inhibitors, such as soluble FMs-like tyrosine kinase 1 (sFLt1) by the placenta in the late stages of pregnancy, seemingly induces endothelial cell dysfunction and apoptosis followed by cardiomyocyte dysfunction. Secretion of sFlt1 is also significantly elevated in preeclampsia, suggesting overlapping cardiotoxic pathophysiology.[180, 181] 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 case of chemotherapeutics.

The outlined angiogenic capacity of the heart is modulated further by signaling pathways that have become additional targets of chemotherapeutics, and in fact, their role for cardiac function has been primarily recognized in the pursuit to define the cardiotoxicity of receptor tyrosine kinase inhibitors, 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 beta (PDGFRβ) as an essential regulator of the angiogenic program in response to hypoxia as well as afterload stress.[182] 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 increased afterload. This coincided with a decrease in myocardial perfusion and a reduction in coronary flow reserve. Myocardial hypoxia and fibrosis was 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).[182] Accordingly, patients with hypertension and myocardial ischemia might be at high risk with drugs that inhibit PDGFRβ signaling such as sunitinib and sorafenib, and intriguingly, this matches clinical observation. However, as these patients are also at risk of developing cardiomyopathy with bevacizumab, the significance of VEGF signaling has to be taken into account. Also, it might be the interplay of 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, e.g. 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.[170] Importantly, loss of pericytes preceded the reduction in

coronary flow reserve and cardiac function, and these consequences were prevented by strategies of pericyte protection, e.g. concomitant thalidomide treatment.[170] These observations are revolutionary as they point out for the first time 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.[183] 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.[184, 185] 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.[186] 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.[187, 188] Intriguingly, patients with CAD and those with diabetes are also at increased risk of anthracycline-induced cardiotoxicity, and provision of neuregulin improves cardiac function after anthracycline-induced myocardial injury.[189] 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 four 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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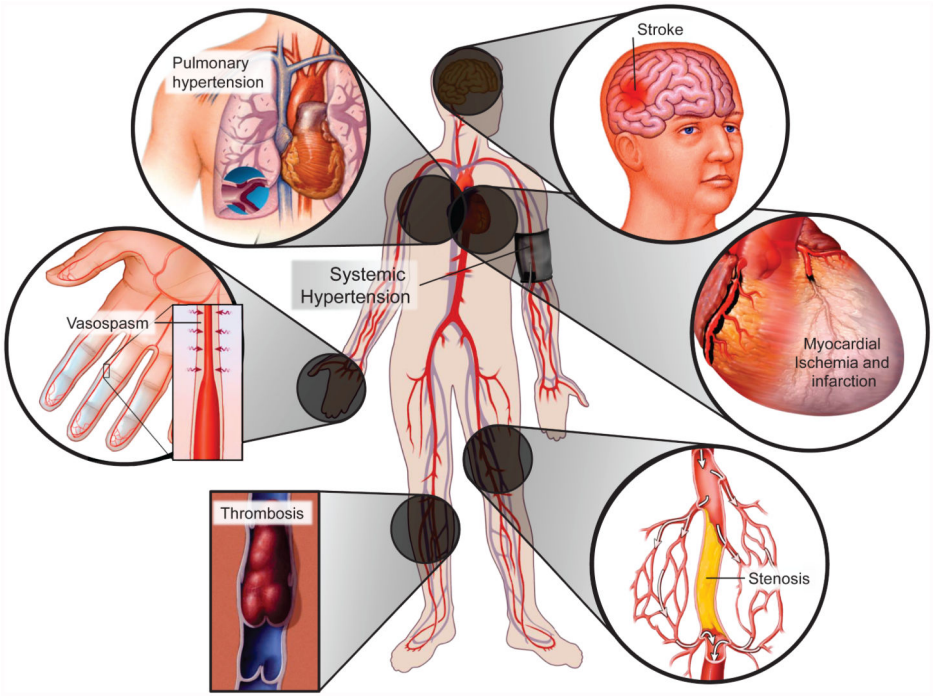

Figure 1.
Simplified spectrum of vascular disease/toxicity induced by chemotherapeutics

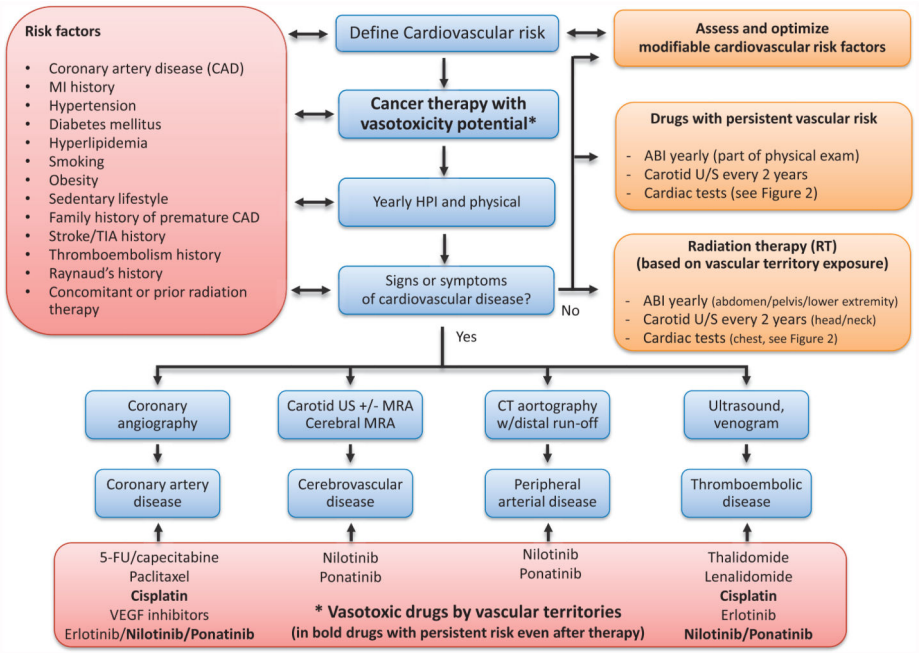

Figure 2.

Algorithm for the comprehensive assessment of cancer patients undergoing chemotherapy with vascular toxicity risk (reproduced, with permission from John Wiley & Sons publications, from Ref. 60).

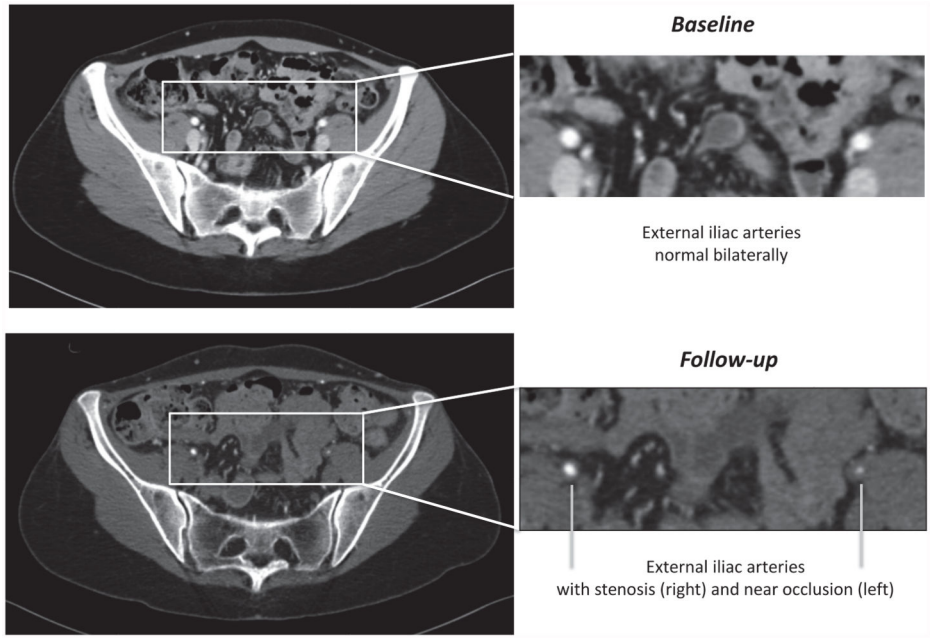

Figure 3.

Example of a case of accelerated peripheral arterial disease of a 32-year-old female without any cardiovascular history but Philadelphia chromosome-positive acute lymphoblastic leukemia. She underwent treatment with dasatinib and subsequently ponatinib, and computed tomography angiography of the abdomen right after treatment did not show any arterial disease (baseline). However, significant changes were noted 20 months later when she presented with critical left limb ischemia. Besides stenosis of the right external iliac artery, near occlusion of the left external iliac artery is noticeable. In fact, diffuse peripheral arterial disease was present. A confounding factor the patient developed acute graft-versus-host-disease but subsequent positron emission tomography imaging remained negative for vasculitis and the interventional report was consistent with atherosclerosis.

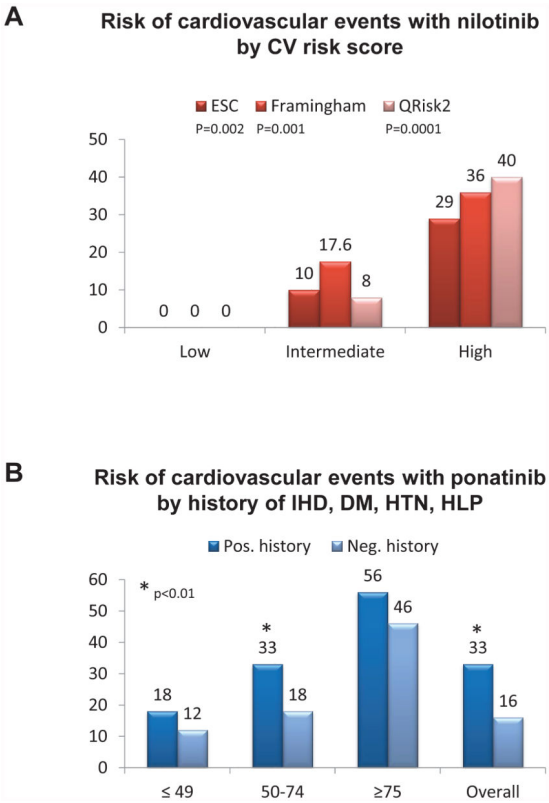

Figure 4.

Illustration of the risk of cardiovascular events with nilotinib (panel A, according to reference 135) and ponatinib (panel B, based on information provided in the Iclusig REMS (Risk Evaluation and Mitigation Strategy) data sheet at http://www.iclusigrems.com).

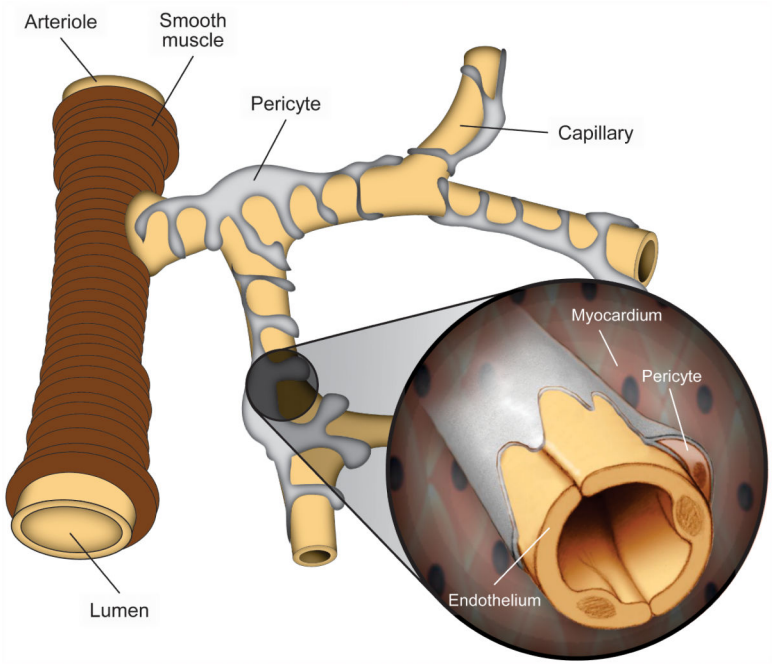

Figure 5.
Illustration of the pericyte structure within the capillary microcirculation of the heart.

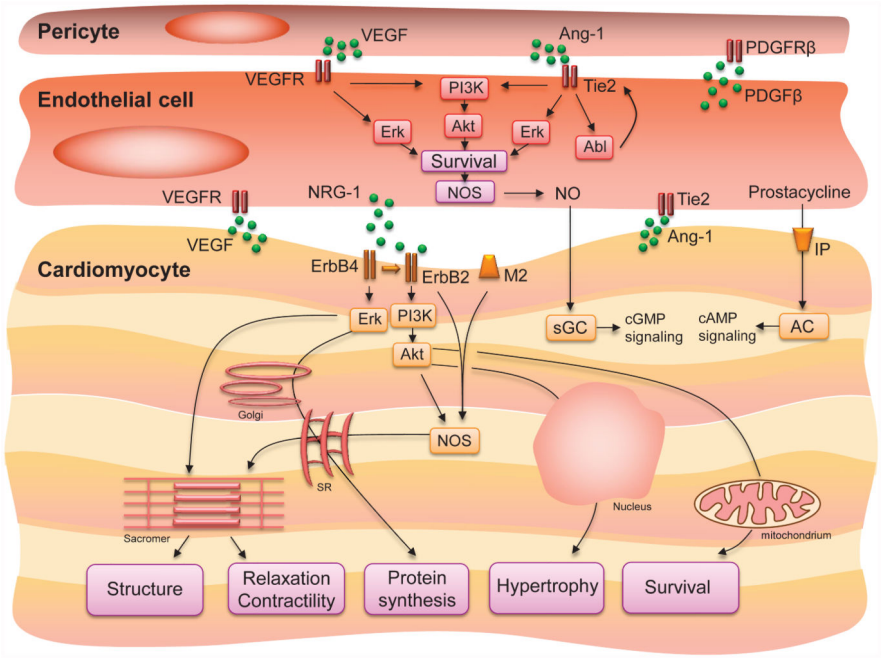

Figure 6.

Schematic presentation of pericyte-endothelial-myocardial interaction. AC = adenylate cyclase, Ang-1 = angiopoietin 1, IP = prostacycline receptor, M2 = muscarinic receptor, NO = nitric oxide, NOS = NO synthase, NRG-1 = neuregulin-1, sGC = soluble guanyl cyclase, PDGR = platelet-derived growth factor, PDGRR = PDGR receptor, VEGF = vascular endothelial growth factor, VEGFR = VEGF receptor.

Table 1

Chemotherapeutics with a prominent vascular side effect profile

	HTN	Angina	AMI	Takotsubo	Raynaud's	Stroke	PAD	Pulm HTN	DVT/PE
Antimetabolites									
5-Flourouracil		X	X	X	X				
Capecitabine		X	X	X	X				
Gemcitabine		X	X		X				
Anti-microtubule agents									
Paclitaxel	X	X	X						X
Alkylating agents									
Cisplatin	X	X	X		X	X	X		
Cyclophosphamide		X						X	
Antitumor antibiotics									
Bleomycin		X	X		X	X		X	
Vinca alkaloids									
Vincristine	X	X	X		X				
mTOR inhibitors									
Everolimus	X	X							X
Temsirolimus	X	X							X
Proteasome inhibitors									
Bortezomib			X			X		X	X
Carfilzomib	X							X	
Vascular disrupting agents									
Combretastatin	X	X	X	X					
Monoclonal antibodies									
Bevacizumab	X	X	X	X		X			X
Ramucirumab	X	X	X			X			
Rituximab	X	X	X	X					
VEGF-receptor fusion molecules									
Aflibercept	X		X			X			X
Tyrosine kinase inhibitors									
Sorafenib	X	X	X			X			X
Sunitinib	X	X	X	X		X			X
Pazopanib	X	X	X			X			X
Axitinib	X	X	X			X			X
Regorafenib	X	X	X						
Cabozantinib	X		X			X			X
Vandetanib	X					X			
Lenvatinib	X		X			X			X
Nilotinib		X	X			X	X		X
Ponatinib	X	X	X			X	X		X

	HTN	Angina	AMI	Takotsubo	Raynaud's	Stroke	PAD	Pulm HTN	DVT/PE
Dasatinib								X	
Miscellaneous									
Interferon-alpha	X	X	X		X	X	X	X	X
Thalidomide									X

AMI = acute myocardial infarction, DVT = deep vein thrombosis, HTN = hypertension, PAD = peripheral arterial disease, PE = pulmonary embolism, VEGF = vascular endothelial growth factor