Mechanisms of Cardiovascular Damage Induced by Traditional Chemotherapy

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Introduction

Chemotherapeutic agents and more targeted drugs, including antiangiogenic drugs targeting vascular endothelial growth factor (VEGF) or its receptors, not only can combat cancer growth but may also cause cardiovascular toxicity and endothelial dysfunction. Continued research efforts aim at better understanding, preventing, and limiting these cardiovascular toxicities. Conventional chemotherapeutic drugs, among which anthracyclines, platinum compounds, and taxanes, and newer targeted agents, such as trastuzumab, bevacizumab, and tyrosine kinase inhibitors, have a well-known risk of cardiovascular toxicity, which can burden their effectiveness by causing increased morbidity and/or mortality. The preservation of cardiovascular function during or following therapies with antineoplastic drugs, without impairing anticancer drug effectiveness, is very important for limiting cardiovascular side effects and preserving cardiovascular health in long-term cancer survivors. Hence, early detection, and prevention and treatment of cardiovascular toxicities are fundamental in order to let oncologic patients complete their lifesaving anticancer therapies.

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Cellular Components of the Cardiovascular System: Cardiomyocytes and Beyond

The myocardium is composed of cardiomyocytes and non-myocytes, fibroblasts and ECs, which are all essential for the function of the healthy heart [1]. In particular, cardiac myocytes produce contractile force, while fibroblasts secrete components of extracellular matrix and paracrine factors, and endothelial cells (ECs) line the coronary vasculature, allowing delivery, via the bloodstream, of free fatty acids and oxygen required to meet the high metabolic demands of contracting myocytes [1, 2]. Additionally, cardiac ECs play a paracrine role. In particular, they release a glycoprotein, neuregulin 1, that binds to ErbB-4, a receptor tyrosine-protein kinase, which in turn heterodimerizes with ErbB2, activating downstream intracellular signaling, including the pathways extracellular

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related kinase1/2 (ERK1/2) and phosphatidylinositol 3-kinase (PI-3K) that regulate contractile function and cardiomyocyte survival and proliferation [3].

In the vasculature, the endothelium has a major role in the regulation of tissue homeostasis, modulating local blood flow and other physiological processes. It is important to preserve a healthy endothelium for the correct homeostasis of the whole cardiovascular system. Indeed, endothelial dysfunction is a hallmark of various pathophysiological conditions, including atherothrombosis, diabetes, sepsis, pulmonary hypertension, microangiopathies associated with neurodegenerative diseases, liver steatosis, and cancer metastasis [4].

Mature ECs, endothelial progenitor cells, and circulating ECs play a role in the physiological maintenance of cardiovascular tissue homeostasis, such as vessel tone, permeability and intima thickness, vessel remodeling and angiogenesis, coagulation, and fibrinolysis. Patients on chemotherapeutic drugs can present with systemic endothelial dysfunction, which enhances cardiovascular disease (CVD) risk and leads to vascular complications [5]. Subjects with cancer and concomitantly impaired systemic endothelial function may be particularly susceptible to the dangerous effects of antineoplastic drugs. Subjects administered with such treatments are often the elderly and exhibit several risk factors such as hypertension, obesity, dyslipidemia, and metabolic syndrome, further deteriorating vascular reserve and leading to enhanced risk of cardiovascular toxicity that can burden anticancer treatments effects because of higher morbidity and mortality [6].

Cardiovascular Toxicity by Chemotherapeutic Drugs

Cardiac Toxicity Induced by Anthracyclines

Cardiovascular and endothelial toxicities are extensively studied; they are due to a combination of "on-target" and "off-target" effects of several antineoplastic treatments. In particular, several drugs are able to perturb a series of signaling pathways that stimulate tumor cell proliferation, but the same pathways are fundamental in maintaining the healthy state of ECs and cardiomyocytes, especially in response to stressful conditions. Hence, a clinical need is the development of novel molecules capable of inducing robust antitumor responses along with minimal systemic collateral effects. Above all chemotherapeutic agents, anthracyclines are well known to induce cardiac dysfunction and HF. Vascular toxicity induced by chemotherapy has historically been less studied; nevertheless, it can lead to enhanced morbidity and/or mortality, thus limiting effectiveness of cancer therapies. Toxic effects of antineoplastic drugs can be very relevant in oncologic patients with endothelial dysfunction. This is particularly true in patients treated with cardiotoxic drugs against cancer, since they are often elderly and have multiple risk factors such as hypertension, obesity, dyslipidemia, and metabolic syndrome, which all lead to a worse vascular reserve, a predisposition to endothelial dysfunction, and vascular damage [6, 7]. Indeed, endothelial dysfunction can be produced virtually by any antineoplastic drug (Table 2.1) [8], with many of them involving ROS production [9, 10]. Such mechanisms dependent on reactive oxygen species (ROS)-mediated pathways were among the first to be linked to endothelial toxicity of chemotherapeu-

Table 2.1 Mechanisms of action and vascular toxicities of the main anticancer drugs

Drugs	Mechanism of vascular toxicity
Anthracyclines	Derangement of NO-dependent function DNA damage, ROS production, caspase 3 and 7 activation, apoptosis
Cisplatin	Enhanced expression of ICAM-1, tPA, PAI-1, CRP, ROS
Taxanes	Cytoskeleton disruption; impairment of proliferation, migration; prothrombotic effect
5-fluorouracil	Blockade of DNA synthesis; disruption of endothelial layer
Trastuzumab	Derangement of endothelial NO generation; alterations of the redox status

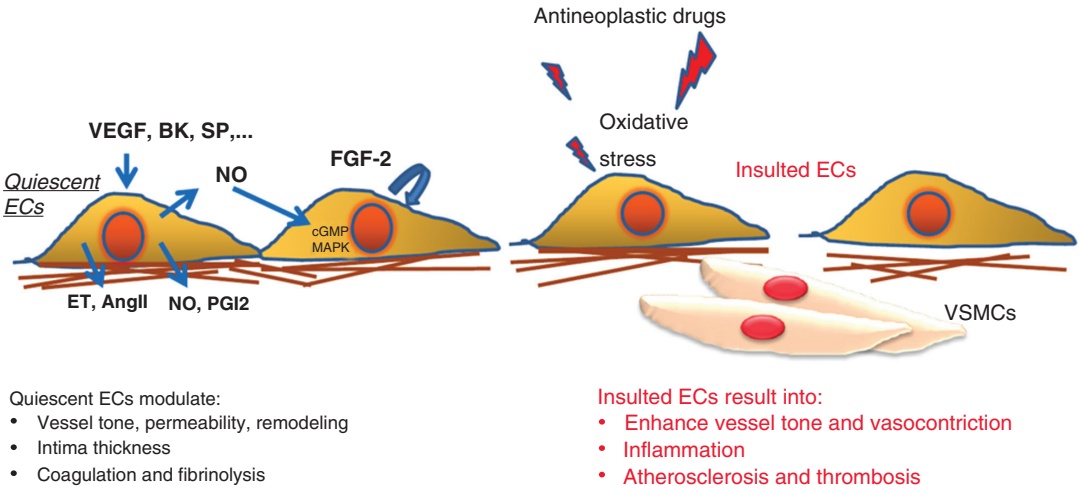

Fig. 2.1 Damages induced by anticancer drugs on endothelial cells. AngII angiotensin II, BK bradykinin, cGMP cyclic guanosine monophosphate, ET endothelin, FGF2 fibroblast growth factor, MAPK mitogen-activated proteine kinase, NO nitric oxide, PGI2 prostacyclin, SP substance P, VEGF vascular endothelial growth factor, VSMCs vascular smooth muscle cells

tics (Fig. 2.1) [10]. In particular, cardiac and endothelial toxicity of *anthracyclines* has been ascribed to redox activation of these drugs to semiquinone intermediates, which can then produce superoxide radicals upon reduction [11]. Both the superoxide anion and its dismutation product—hydrogen peroxide—are characterized by some level of toxicity [12]. Anthracyclines are antineoplastic drugs originally derived from *Streptomyces*. Anthracyclines are red, aromatic polyketides and exist in different forms due to the structural differences in the aglycone and the different sugar residues attached [13]. Among the several pathways that are supposedly involved in cytotoxicity of this class of anti-antineoplastic compounds, accumulation in the nucleus of neoplastic and proliferating cells, DNA intercalation, interaction with/inhibition of DNA-binding proteins (such as topoisomerase II-TopII, RNA polymerase, histones), ROS production, and antiangiogenic mechanisms [14] are considered to be the most relevant.

Cardiovascular toxicity provoked by anthracyclines is a complex phenomenon, influenced by several mechanisms that include drug accumulation in nuclei [15] and mitochondria [16] and DNA repair [17], stress-induced signaling pathways [18], sarcoplasmic reticulum stress [19], nitrosative stress [20], the activity on drug transporters (including MDR1 and MRP1) [21], drug metabolism [22], and TopI and II inhibition [16, 23]. In particular, TopII is a cellular target of anthracyclines [23]. In mammals, there are two isoenzymes of TopII: TopIIa and TopIIb. TopIIa is expressed only in proliferating cells such as tumor cells [24] and is thought to be the molecular basis for anthracyclines' anticancer effects. TopIIb is a ubiquitous isoform highly expressed in terminally differentiated cells, including adult cardiomyocytes [25] and endothelial cells [26]. Thus, the interaction between anthracyclines and TopIIb may directly induce endothelial toxicity and LV dysfunction [25].

Recent evidence showing that pixantrone, a novel anthracycline used in refractory-relapsed non-Hodgkin lymphoma, ineffective on TopIIb, does not cause endothelial toxicity and cardiomyopathy, further supports the hypothesis that inhibition of TopIIb is a key player in the generation of anthracycline toxicity [27]. However, pixantrone has different functional properties compared to anthracyclines, with specific toxicities [28]. A deeper knowledge into these mechanisms will help design a rational strategy to fight endothelial toxicity of anthracyclines. A valid alternative is the use of liposomal doxorubicin,

which is associated with lower cardiac toxicity [29]. This formulation seems also to be safer on the endothelial side, with lower caspase-3 activation and concomitant preservation of anti-apoptotic protein Mcl-1 expression in cultured ECs, as compared with doxorubicin [30].

In addition, anthracyclines also seem to cause negative arterial remodeling. Indeed, acute changes in pulse wave velocity (PWV) and arterial distensibility have been observed in breast cancer patients treated with anthracyclines, and such changes partially reversed after therapy discontinuation [31]. Higher arterial stiffness was also shown in childhood cancer survivors who had undergone chemotherapy [32].

Cardiac Toxicity Induced by Other Chemotherapeutic Drugs

A widely used antimetabolite is the pyrimidine analogue *5-fluorouracil* (5-FU) that fights cancer proliferation by several mechanisms, among which are inhibition of thymidylate synthase by 5-fluoro-2′-deoxyuridine-5′-monophosphate, incorporation of 5-fluorouridine-5′-triphosphate into RNA, and incorporation of 5-fluoro-2′-deoxyuridine-5′-triphosphate into DNA [33]. 5-FU has a brief half-life; nevertheless, active metabolites are retained in all tissues, including heart and tumor cells, resulting in a prolonged exposure of cells to the drug [9, 34–36]. 5-FU is able to inhibit the angiogenic process by antagonizing the stimulatory effect of vascular endothelial growth factor (VEGF) on DNA synthesis during endothelial cells (EC) mitosis [37] and generates ROS-induced endothelial damage [38]. Although a therapeutic approach to starve tumors and decrease their progression can be achieved through inhibition of EC proliferation during tumor angiogenesis, inhibiting systemic VEGF also leads to alterations of endothelial cell homeostasis, increasing the risk of atherogenesis and arterial thromboembolic events, often leading to coronary vasospasm and myocardial infarction, cerebrovascular insults, and peripheral or mesenteric ischemia [39–41]. Hence, protecting endothelial cell function may be of some importance during administration of 5-FU. Among other mechanisms that have been hypothesized are impairment of generation of nitric oxide (NO) that can lead to coronary spasms and endothelium-independent vasoconstriction [9, 42, 43]; enhanced intracellular levels of ROS/RNS, leading to oxidative stress and myocyte apoptosis [44]; and interference with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA [9].

Capecitabine is a prodrug that is transformed enzymatically to 5-FU by thymidine phosphorylase after oral intake [7]. This key enzyme is highly expressed in both atherosclerotic plaques and cancer tissues, explaining the higher prevalence of CTX from capecitabine in patients with coronary artery disease (CAD). *Capecitabine* may impair vascular biology profoundly; nevertheless, this toxicity is much milder than 5-FU, resulting in uncommon cardiotoxic side effects. Other possible mechanisms include endothelial dysfunction with thrombosis, direct damage of myocytes, and hypersensitivity reaction with Kounis syndrome [7, 45]. The main pathophysiologic explanation for the cardiotoxicity of 5-fluorouracil has been the adverse effects on coronary circulation. This may also be considered the underlying mechanism of presentation of apical ballooning syndrome described with various chemotherapeutic agents.

A synergistic effect between capecitabine and other antineoplastic agents has also been hypothesized. Cardiotoxicity has been shown to be more frequent in patients treated with capecitabine in addition to either taxanes or lapatinib than in patients treated with capecitabine alone [9, 46–49].

Interestingly, a single high dose of capecitabine was able to cause hemorrhagic infarction of the LV in rabbits, with proximal spasms of the coronary arteries, and death within a few hours from intravenous injection. In contrast, repeated lower doses led to cardiac hypertrophy, concentric fibrous thickening of the coronary intima, and foci of necrotic cardiomyocytes [50].

Other anticancer drugs such as *cisplatin*, often used in combination with bleomycin and vinca alkaloids, can produce cardiovascular toxicity

including acute coronary thrombosis and may be linked to higher long-term cardiovascular risk [51]. Cisplatin and most other platinum-based drugs are simple inorganic molecules containing a platinum ion. Tumor apoptosis and, unfortunately, also myocardial ischemia can be caused by these drugs via stimulation of signal transduction that finally activates mechanisms involving death receptor as well as mitochondrial pathways. The characteristic nephrotoxicity, ototoxicity, and most other cytotoxicities caused by platinum compounds can be ascribed to apoptosis. In endothelial cells, cisplatin can provoke cytotoxicity by means of enhanced production of procoagulant endothelial microparticles [52] and free radicals [53, 54]. Indeed, higher plasma levels of the endothelial prothrombotic markers vWF and PAI-1 were present in testicular cancer patients administered with cisplatin, in comparison to subjects who underwent orchiectomy alone [55]. In addition, a study from Vaughn and coworkers [56] found that in long-term cancer survivors who had been administered with cisplatin-based regimens, there was a derangement in NO-dependent vasodilation (flow-mediated vasodilation) in the brachial artery, compared to chemotherapy-naïve subjects. On such basis, subjects who underwent therapies with alkylating agents such as cisplatin would benefit from the administration of antiplatelet or anticoagulant or antithrombotic drugs in order to protect vascular function, thus preserving cardiovascular health [55, 56]. Interestingly, recent evidence shows increased platelet activation in cancer (e.g., colon cancer), with a lower incidence and mortality for colon cancer in patients on low doses of aspirin [57]. Ongoing primary prevention and adjuvant trials (e.g., ADD-Aspirin Trial) of low-dose aspirin will be of help to investigate the contribution of this strategy on chemotherapy-associated vascular toxicity.

Taxanes are diterpenes produced by the plants of the genus *Taxus*. They inhibit cell division, chromatid separation, and growth, thus leading to cell death. These microtubule-binding drugs are generally known as mitotic inhibitors or microtubule inhibitors. As for several tumors, taxanes harm endothelial cell functions, such as proliferation and invasion [58]. In addition, the taxane paclitaxel also augments endothelial tissue factor (TF) expression via its stabilizing effect on microtubules and stimulation of c-jun kinase (JNK), thus leading to downregulation of thrombomodulin and increased protein nitration [59]. It has been demonstrated that another tubulin blocker, vincristine, is able to adversely affect rat cardiac microvascular ECs [7, 60].

Cardiovascular damage has also been reported for other classical chemotherapeutics, such as *cyclophosphamide* (a nitrogen mustard inducing DNA alkylation) [61], *bleomycin* (antitumor antibiotic inducing DNA degradation), and *vinca alkaloids* (depolarizing agents causing spiral-like distortions of the cellular microtubules) [7, 62].

Vascular Toxicity Induced by Chemotherapy

First, it has to be kept in mind that it usually takes many years for atherosclerotic processes to become symptomatic. This latency might contribute to the fact that the effects of anticancer drugs on blood vessels are not clear yet. In addition, smoking and dyslipidemia are main risk factors for both cancer and atherosclerosis [63]. Also, the co-prevalence of different cancers and clinical manifestations of atherosclerosis complicate the distinction between toxic side effects of chemotherapy and preexisting cardiovascular risk. Of notice, anticancer drugs such as cisplatin, bleomycin, and etoposide cause a higher long-term risk for vascular and atherosclerotic complications [64, 65]. Such long-term effects have to be separated from acute vascular events induced by arterial thrombosis, which might provoke thrombotic occlusion of coronary vessels even with no sign of coronary artery disease [62]. Vascular spasm and Raynaud phenomenon, angina pectoris, and even myocardial infarction can be caused by 5-FU and capecitabine or paclitaxel, gemcitabine, rituximab, and sorafenib [66–68]. In addition, cisplatin, bevacizumab (angiogenesis inhibitor), tamoxifen (selective estrogen receptor blocker), and sunitinib and sorafenib (tyrosine kinase inhibitors) can cause an enhanced incidence of VTE [69–72].

5-fluorouracil (5-FU) can provoke chest pain in 1–18% of subjects who are administered with this drug, with its oral prodrug capecitabine at a 50% lower rate. The onset can be pretty quick (as systemic peak levels are reached) and is linked to deranged vascular reactivity [51, 73, 74]. Chest pain can manifest as exertional angina and abnormal noninvasive stress testing [75] but also as resting or variant angina. This is due to the fact that these drugs primarily alter molecular signaling pathways modulating vascular smooth muscle cell tone, thus causing vasoconstriction [51, 75].

Taxanes can also cause similar types of chest pain. In particular, paclitaxel induces chest pain with an incidence of 0.2–4% [51, 68, 76, 77]. As for 5-FU, a major role is believed to be played by vasoconstriction (spasm). Differently from 5FU, though, taxanes can induce alterations of heart rhythm with a higher incidence [76].

Cisplatin, especially when administered with bleomycin and vinca alkaloids, can cause chest pain at an incidence as high as 40% [78–83]. Endothelial dysfunction is the major mechanism of deranged vasoreactivity [84].

Beside chest pain, oncologic patients treated with 5-FU and capecitabine can even present with acute coronary syndromes (ACS) and can show the entire spectrum from unstable angina to acute myocardial infarction (AMI) and also arrhythmic complications such as ventricular tachycardia and fibrillation leading to sudden death, according to the intensity and duration of vasoconstriction [85–87]. ACS presentations of paclitaxel, gemcitabine, rituximab, and sorafenib have also been ascribed to vasoconstrictive pathophysiology [66–68, 77, 88, 89]. In oncologic patients with significantly lowered myocardial reserve, ACS and AMI can be caused by tachycardia, hypotension, hypoxia, and anemia because of coronary artery disease or potentially pathoanatomic variants such as myocardial bridging or as the result of the well-established types of plaque complications [51].

Oncologic patients treated with vasculotoxic chemotherapeutics such as cisplatin (with and without bleomycin and vinca alkaloids) may also present with a greater propensity toward erosion [51]. Indeed, angiography may reveal single or multivessel coronary thrombosis even without evidence of atherosclerosis [62, 90–95]. Erosion as the leading mechanism is supported by experimental evidence showing induction of endothelial damage with activation of apoptosis and stimulation of thromboxane generation, platelet activation, and aggregation [90, 92, 96, 97]. Accordingly, these acute coronary events are unpredictable. Interestingly, cisplatin levels can be detected for years after therapy, and this is paralleled by a high risk for chest pain episodes and acute ischemic events [51, 98].

Beside typical scenarios of ACS, oncologic patients can also undergo apical ballooning syndrome, precipitated by several factors, among which is the exposure to various and significant stressors [99]. In particular, this syndrome has been noted in patients treated with 5-FU, capecitabine, cytarabine, axitinib, sunitinib, bevacizumab, rituximab, trastuzumab, and combretastatin [100–109]. In 38 subjects with cancer and stress cardiomyopathy seen at the MD Anderson Cancer Center, female sex (76%), advanced age (65.9 ± 9 years), and advanced cancer were the main patient characteristics [110]. Most of the events occurred in close temporal proximity to three kinds of tumor interventions: surgery, stem cell transplantation, and chemotherapy. Importantly, in this latter group, 64% were able to resume different anticancer drugs on cardioprotective therapies within 1 month with no recurrence. Although the exact pathophysiology of apical ballooning syndrome is still unclear, one possible explanation is abnormal coronary vasoreactivity caused by the aforementioned chemotherapeutics. Interestingly, a subject who exhibited apical ballooning with 5-FU, for instance, showed abnormal coronary vasoresponse to acetylcholine, with paradoxical vasoconstriction following 5-FU [75, 111]. Similarly, the response to catecholamines might be also altered, and coronary microcirculation might also be involved in changes in vasoreactivity, thus leading to abnormalities in perfusion and contraction [99, 112, 113].

Cancer patients can also present with limb ischemia. The primary presentation of limb isch-

emia in these patients has been Raynaud's that can also lead to ischemic fingertip necrosis. The incidence can be as high as 30% and may be a signal systemically abnormal vasoreactivity and even myocardial infarction risk [82, 83]. This complication has been reported for bleomycin, vinca alkaloids, cisplatin, carboplatin, gemcitabine, and interferon-α.29 [114–117]. For bleomycin, Raynaud's can be apparent as early as after the first dose and is likely linked to a direct effect on the endothelium [118]. For other drugs, e.g., interferon-α, the mechanisms seem to be more complex, including vasospasm, thrombus formation, and immune-mediated vasculitis [119]. Importantly, it also has to be acknowledged that Raynaud's can also occur as a paraneoplastic phenomenon, even before the diagnosis of a tumor or its recurrence [120].

Stroke and transient ischemic attack can appear in oncologic patients with patterns and risk factors similar to non-cancer patients. Cancer patients are already at higher risk for thromboembolic events, including those related to paradoxical embolization and indwelling catheters [51, 121–123], with a major role that can be played by hypercoagulability in some subjects [124]. 5-FU and cisplatin have been linked with a higher risk of stroke [125–128]. In particular, endothelial cell death caused by cisplatin may generate not only local but also possibly even systemic vulnerability by the generation of procoagulant microparticles [129]. This may explain why, in some cases, no cause of ischemic stroke can be identified, while, in other cases, local cranial arterial thromboses can even cause acute complete occlusions [51, 130].

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