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Review

Anticancer therapy-induced vascular toxicity: VEGF inhibition and beyond

Daniela Di Lisi [a], Rosalinda Madonna [b,c,*], Concetta Zito [d], Enrico Bronte [e], Giuseppe Badalamenti [e], Paolo Parrella [f], Ines Monte [g], Carlo Gabriele Tocchetti [f], Antonio Russo [e], Giuseppina Novo [a]

[a] Division of Cardiology, Department of Internal Medicine and Specialties, University of Palermo, Palermo, Italy
[b] Center of Excellence on Aging, Institute of Cardiology, "G. d'Annunzio" University - Chieti, Chieti, Italy
[c] Texas Heart Institute and University of Texas Medical School in Houston, Cardiology Division, Houston, TX, USA
[d] Cardiology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[e] Department of Surgical, Oncological and Stomatological Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy
[f] Department of Translational Medical Sciences, Division of Internal Medicine, Federico II University, Naples, Italy
[g] Department of General Surgery and Medical-Surgery Specialties, University of Catania, Catania, Italy

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ABSTRACT

Cardiotoxicity induced by chemotherapeutic agents and radiotherapy is a growing problem. In recent years, an increasing number of new drugs with targeted action have been designed. These molecules, such as monoclonal antibodies and tyrosine kinase inhibitors, can cause different type of toxicities compared to traditional chemotherapy. However, they can also cause cardiac complications such as heart failure, arterial hypertension, QT interval prolongation and arrhythmias. Currently, a field of intense research is the vascular toxicity induced by new biologic drugs, particularly those which inhibit vascular endothelial growth factor (VEGF) and its receptor (VEGF-R) and other tyrosine kinases. In this review, we aim at focusing on the problem of vascular toxicity induced by new targeted therapies, chemotherapy and radiotherapy, and describe the main mechanisms and emphasizing the importance of early diagnosis of vascular damage, in order to prevent clinical complications.

1. Introduction

In recent years, with the introduction of new drugs in therapeutic regimens, we have assisted to significant advances in the treatment of cancer. Among these drugs, monoclonal antibodies such as trastuzumab, pertuzumab and bevacizumab, and tyrosine kinase inhibitors-TKI (i.e. sorafenib, sunitinib, imatinib, lapatinib, axitinib, pazopanib, cabozantinib) are often used. Such molecules are characterized by a targeted action [1] on well-known proteins with important roles in cancer biology [2]. However, despite their selective action, they can still cause cardiovascular complications such as arterial hypertension, QT interval prolongation, heart failure (HF), cardiomyopathy, stroke, acute myocardial infarction (AMI), thromboembolic events and cardiovascular deaths [3,4] since the same targets also play a role in maintaining cardiovascular homeostasis [5–9].

As their effects on the cardiovascular system are not a so-called "class-effect", for the majority of the approved TKIs the risk of significant cardiotoxicity appears to be low. However, for some of them, this risk can become significant because of their long-term and continued use.

Many studies have focused on the myocardial effects of targeted therapies. The purpose of this review is twofold, that is to discuss the major mechanisms of vascular toxicity induced by new targeted therapies in parallel with chemotherapy and radiotherapy, and to highlight the importance of an early diagnosis of vascular damage, in order to prevent cardiovascular complications.

2. Endothelial function and VEGF

It is now well accepted that the endothelium is not a simple cellular monolayer that separates the blood from vascular walls, but also plays a key role in maintaining vascular homeostasis, by producing vasoconstrictor and vasodilator substances, such as endothelin-1 (ET-1), angiotensin II (Ang II), thromboxane A2, reactive oxygen species, nitrogen monoxide (NO) and prostacyclin [10]. The homeostasis of the entire cardiovascular system is maintained with the help of a healthy endothelium. Mature endothelial cells (ECs), endothelial progenitor cells and circulating ECs participate in the physiological maintenance of cardiovascular tissue homeostasis, including vascular tone, permeability and intima thickness, vessel remodeling and angiogenesis, coagulation

* Corresponding author at: Center of Excellence on Aging, Institute of Cardiology, "G. d'Annunzio" University - Chieti, 66100 Chieti, Italy.
E-mail address: rmadonna@unich.it (R. Madonna).

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and fibrinolysis. In contrast, endothelial dysfunction is involved in the pathophysiology of several diseases, including atherothrombosis, diabetes, sepsis, pulmonary hypertension, microangiopathy associated with neurodegenerative diseases, hepatic steatosis and cancer metastasis [11,12].

Vascular endothelial grown factor (VEGF) is the main member of a family of structurally and functionally related cytokines, which plays a critical role in angiogenesis, promote cell survival, and growth and proliferation of endothelial cells by binding to specific receptors (VEGFR-1, VEGFR-2, neuropilin) [13,14]. VEGF includes a family of seven members such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F and PIGF. They all have a common homologous domain. VEGF-A is the most representative compound. VEGF-A mRNA is expressed in several tissues, including the lung, kidney, heart and adrenal glands. VEGF-A is a glycoprotein that exists in at least seven isoforms, from 34 to 42 kDa of molecular weight, which are derived by alternative splicing of the eight exons of the VEGF human gene. The monomers consisting of 121, 145, 148, 165, 183, 189 or 206 amino acids and the presence or absence of the heparin binding domain affects the characteristics of the different isoforms. VEGF 189 and VEGF 206 bind heparin with high affinity, are strongly basic and completely sequestered in the extracellular matrix, while VEGF 121 is a highly diffusible protein. VEGF 165 has intermediate properties.

To date, researchers have identified three different receptors that bind VEGF, such as VEGFR-1 (Flt-1), VEGFR-2 (KDR or Flk-1) and VEGFR-3. The binding of VEGF to its receptors promotes the growth of vascular endothelial cells derived from arteries, veins and lymphatic vessels. Each receptor has seven immunoglobulin-like domains in the extracellular portion, a single transmembrane portion and an intracellular tyrosine kinase domain. The different receptors differ in activity and affinity for ligand:

a) VEGFR-1 (Flt-1): it is the first VEGF receptor discovered, although its function is not yet clear. The binding of VEGF-A with this receptor seems to modulate the division of endothelial cells during the early stages of vascular development, although with a weak activity [5,15–17].
b) VEGFR-2 (KDR or Flk-1) appears to be the most important receptor in the regulation of mitogenesis and permeability by VEGF. The effects of VEGF binding to VEGFR-2 during angiogenesis include the production of platelet activating factor by endothelial cells, stimulation of mitosis and migration of these cells, as well as an increase in vascular permeability. It has been shown that Flk-1 null mice are characterized by the absence of vasculogenesis. This evidence highlights the importance of VEGF binding to VEGFR-2. VEGF binding to this receptor leads to activation of inositol 3 phosphate kinase, which results in an increase in intracellular inositol triphosphate. This event leads to activation of protein kinase B (Akt/PKB) and endothelial nitric oxide synthase. The first enzyme inhibits caspase-9, promotes cell survival, while the second enzyme leads to NO formation which, in turn, increases the permeability and cell migration [18].
c) The receptor VEGFR-3 differs from the other two because it moves towards proteolytic cleavage of the extracellular portion. Only VEGF-C and VEGF-D bind to this receptor, and its presence is limited to the endothelial cells of lymphatic vessels [18–19].

3. Vascular damage caused by VEGF/VEGFR pathway inhibition

Many of the new biological drugs can cause heart and vascular damage. The mechanisms of the underlying cardiovascular toxicity can be attributed to two main types of toxicity. The first is on-target toxicity (also known as mechanism-based or target related), due to inhibition of target kinases expressed in other organ systems such as the heart and vasculature. On-target toxicity typically occurs with imatinib, by inhibition of platelet-derived growth factor receptors (PDGFRs), c-kit, Src family member Lck, CSF1R, Cdc2, and discoidin domain receptor (DDR)1. The second type of toxicity is off-target toxicity. In this case, cardiovascular toxicity occurs because the drug inhibits a kinase that is not among its "planned" targets, which, unfortunately, also plays a key role in heart and vasculature. The inhibition of AMP-activated protein kinase (AMPK) by Sunitinib is an example of off-target toxicity.

The inhibition of VEGF and its receptors represents a main (but not sole) mechanism by which antiangiogenic drugs can cause vascular toxicity [20]. Among them, *bevacizumab* is a monoclonal antibody that targets VEGF-A, thus preventing its interaction with VEGFR and leading to inhibition of tumor angiogenesis. It can cause high blood pressure, left ventricular dysfunction (LV), HF, myocardial ischemia and atherothrombotic events (ATEs). The incidence of severe ATEs in patients treated with bevacizumab was reported at around 1.8%, with an incidence of AMI equal to 0.6% [21]. *Sunitinib* is a multi-target TKI. It targets the VEGF receptor (VEGFR) 1–3, PDGFR, c-Kit, FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor-1 receptor (CSF-1R), and the product of the RET human gene (RET, mutated in medullary thyroid carcinomas/multiple endocrine neoplasia). It can cause high blood pressure and HF [22]. *Sorafenib* is a multi-target TKI that, at clinically relevant concentrations in in vitro kinase assay, inhibits at least 15 kinases, including VEGFR, PDGFR, Raf-1, B-Raf, c-Kit, and FLT3 [23,24]. It can cause high blood pressure, myocardial ischemia and rarely HF [25]. *Pazopanib* is a small molecule, multi-target inhibitor of PDGFR, VEGFR, and c-KIT. It can cause high blood pressure and congestive HF [26,27]. *Axitinib* is a potent second generation inhibitor of VEGFR. It can cause high blood pressure, but also myocardial infarction and arrhythmias [28]. *Regorafenib* is a multi-target TKI. It targets VEGFR 2–3, RET, KIT, PDGFR, and RAF. It can cause high blood pressure and myocardial ischemia [24,29]. *Cabozantinib* is a potent inhibitor of receptor tyrosine kinases, including VEGF, MET, RET, KIT, Flt-3, AXL and Tie-2. It can cause venous thrombosis and arterial thrombosis rarely (myocardial infarction and stroke [30], see Table 3).

In addition, new TKIs are used to treat chronic myeloid leukemia, such as nilotinib, dasatinib and ponatinib. In particular, nilotinib and ponatinib can cause cardiovascular toxicity and thrombosis [31]. *Nilotinib* inhibits Bcr-Abl, PDGF, cKit, BCR-ABL, PDGFR, c-KIT, CSF-1R, and DDR1. It can accelerate atherosclerosis and peripheral arterial occlusive disease (PAOD), and can determine QTc prolongation [32]. The exact mechanism is not known. *Ponatinib* inhibits Bcr-Abl T315I, Src SFKs, and Src e Lyn. It can cause high blood pressure and cardiovascular events [33]. *Dasatinib* inhibits BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. It can cause pleural effusion, heart failure, and pulmonary hypertension [34].

Overall, there are substantial differences in the incidence of cardiovascular side effects of VEGF-inhibitors (i.e., sunitinib - high incidence - vs. sorafenib - low incidence) and BCR-ABL inhibitors (i.e., ponatinib - high incidence - vs. nilotinib - low incidence).

VEGF cascade induces proliferation of endothelial cells and promotes vascular integrity. Hence, inhibition of VEGF/VEGFR signaling pathway seems to be the main cause of vascular injury, endothelial dysfunction and atherothrombotic events [35]. In fact, VEGF/VEGFR inhibition can lead to endothelial dysfunction and exposure of subendothelial collagen. This can facilitate the activation of the coagulation cascade by tissue factor binding and occurrence of thrombotic events. When VEGF interacts with its receptors VEGFR1, VEGFR2 and VEGFR3, PI3K and phospholipase C (PLC) are triggered. On the one hand, PI3K induces the conversion of PIP2 into PIP3, which stimulates Akt supported by the action of PD1K. Akt then determines the stimulation of eNOS (endothelial nitric oxide synthase), thus causing the production of NO. On the other hand PLC determines the cleavage of PIP2 to inositol trisphosphate (IP3) and diacylglycerol (DAG). The second messenger IP3 facilitates the entry of Ca^{2+} ions in the cell. This can lead to eNOS induction and increase of NO production. NO can increase cGMP production through induction of guanylyl cyclase activity. This produces vasodilation with a reduction of platelet aggregation and smooth muscle cell growth.

Thus, anti-VEGF therapies promote an unbalance between vasodilation and vasoconstriction through the reduction of NO and prostacyclin, and increase the viscosity of the blood through the overproduction of erythropoietin. Vasoconstriction is accompanied by endothelial dysfunction. These are two basic elements for creating an altered state of perfusion. Hence, increased blood viscosity related to cancer, inhibition of the VEGF/VEGFR and endothelial dysfunction are cardiovascular risk factors that contribute to increasing the risk of arterial thrombosis (stroke and myocardial infarction) in cancer patients.

Mechanisms of high blood pressure include both functional (inactivation of eNOS and production of vasoconstrictors such as endothelin-1) and structural (capillary rarefaction) modifications [36]. Probably VEGF-mediated suppression of nephrin, which is important for the maintenance of glomerular function, can contribute to the development of arterial hypertension [37]. The loss of pericytes due to inhibition of PDGFR, along with inhibition of angiogenesis, due to the VEGFR inhibition, are supposed to be the main mechanisms for capillary rarefaction [38]. In addition, vascular injury can be "direct", i.e. caused directly by the target therapies and VEGF/VEGFR or other inhibitory molecules, or "indirect" i.e. caused by arterial hypertension secondary to target treatment.

4. Vascular damage induced by inhibition of other kinases than VEGFR

PDGFR inhibition is known to impair angiogenesis, and leads to microvascular dysfunction through the loss of pericytes [39]. This could be another mechanism related to vascular toxicity induced by sunitinib and other target drugs. Other molecules involved in angiogenesis could have important role in the genesis of vascular damage after their inhibition. For example, some studies have investigated the role of Notch in the cardiovascular system. Inhibition of Notch is effective in the oncology setting because it can result in poor highly proliferative tumor cells and also inhibits the survival of cancer stem cells, which are considered to be responsible for relapse and metastasis. Furthermore, since Delta-like ligand 4 (Dll4)-activated Notch signaling is an important modulator of angiogenesis, anti-Dll4 agents are under investigation to reduce vascularization of the tumor. Notch plays an important role in the heart during the development and, after the birth, in response to cardiac damage. Therefore, agents used to inhibit Notch in tumors (gamma secretase inhibitors and anti-Dll4 agents) could potentially affect myocardial repair. Inhibition of Notch signaling may lead to either cardiomyocyte or endothelial dysfunction [40]. Notch plays an important role in protecting endothelial cells from apoptosis induced by conditions such as inflammation, oscillatory blood flow, and ischemia [41].

Another important target is represented by the human epidermal growth factor receptor-2 (Her-2) also called ErbB2, even if the risk of significant cardiotoxicity by anti-Her-2 drugs appears to be low. ErbB2 is a transmembrane glycoprotein receptor which plays a key role in cell growth, including myocyte growth, and inhibition of apoptosis [7–9,42]. Cardiac endothelial cells produce the growth factor NRG1, which activates the Her-2/Her-4 complex, thus triggering cascades of ERK–MAPK and PI3K–Akt signaling pathways, promoting cell survival [43]. Importantly, NRG-1 regulates angiogenesis and NOS-dependent desensitization of adrenergic stimulation. Trastuzumab treatment acts on Her-2 reduce survival signals and induce mitochondrial dysfunction and depletion of energy supplies. In addition, stress factors, such as previous treatment with anthracyclines, increase the production of reactive oxygen-species (ROS) [44]. Under normal conditions, cells restrict this event by overexpressing Her-2 and so leading to the activation of the cell survival pathways. The Her-2 blockage does not allow the activation of these pathways that create a state resulting from oxidative stress leading to apoptosis [5,64,5–51]. Importantly, ErbB2 inhibition has been also shown to be responsible for a loss of vascular function due to the reduction in bioavailability of nitric oxide (NO), the increase in ROS generation and the reduction of survival signals [52,53].

5. Vascular damage caused by chemotherapy

Chemotherapy-induced cardiotoxicity has been extensively studied. Above all chemotherapeutic agents, it is well known that *anthracyclines* induce left ventricular dysfunction and HF. Vascular toxicity induced by chemotherapy is poorly analyzed; however, it can be responsible for increased morbidity and/or mortality, thus limiting effectiveness of cancer therapies. Cancer patients with endothelial dysfunction, may be particularly susceptible to the adverse effects of anticancer medications. This is confirmed by the fact that patients treated with cardiotoxic therapies against cancer, often have multiple risk factors such as hypertension, obesity, dyslipidemia and metabolic syndrome, which all lead to a worse vascular reserve, predisposing to endothelial dysfunction and vascular damage [54].

Endothelial dysfunction can be produced by any chemotherapeutic agent [55], with many of them involving the production of ROS [56]. For instance, cardiac and endothelial *anthracyclines* toxicities were attributed to the activation of redox drugs to semiquinone intermediates, which generate superoxide radicals upon reduction. Both the superoxide anion and its dismutation product, hydrogen peroxide, are in fact toxic for the endothelium [57,58]. Endothelial toxicity induced by anthracyclines seems to be influenced by several mechanisms, such as drug accumulation in the nuclei, mitochondria, DNA repair, stress-induced signaling mechanisms, the sarcoplasmic reticulum stress, nitrosative stress, the activity on drug transporters (including MDR1 and MRP1), drug metabolism, and TopI and II inhibition [59,60]. The latter is a cellular target for anthracyclines. The ubiquitous TopIIb is expressed in terminally differentiated cells, including adult endothelial cells; [61] hence it was recently shown that TopIIb could be responsible for the development of anthracycline-induced endothelial toxicity and cardiomyopathy [62].

Anthracyclines are also considered to cause negative arterial remodeling. As a result, the acute changes in Pulse Wave Velocity [PWV] and arterial distensibility were observed in breast cancer patients treated with anthracyclines. In addition, these changes partially reverse after therapy discontinuation [63]. An increase in arterial stiffness was also demonstrated in childhood cancer survivors following chemotherapy [64].

Among other chemotherapeutic drugs, *cisplatin* is able to cause myocardial ischemia and tumor apoptosis [65]. Apoptosis is also responsible for the typical nephrotoxicity, ototoxicity and other cytotoxicities. Cisplatin-induced cytotoxicity in endothelial cells has been linked to increased generation of procoagulant endothelial micro-particles and free radicals [66,67]. For example, testicular cancer patients treated with orchiectomy showed a decrease in plasma levels of the endothelial pro-thrombotic markers PAI-1 (plasminogen activator inhibitor-1) and vWF (Von Willebrand factor) compared to those patients treated with cisplatin [68]. In addition, NO-dependent vasodilation (flow-mediated vasodilation) seems to be compromised in the long-term cancer survivors who received cisplatin-based chemotherapy compared to chemotherapy-naive patients [69].

The chemotherapeutic agent *5-fluorouracil* (5-FU) can cause myocardial ischemia and coronary vasospasm is the main underlying mechanism, which has been postulated (Table 1). Its oral form capecitabine is a prodrug that, after oral intake, is transformed enzymatically to 5-FU by thymidine phosphorylase. Although capecitabine may have profound effects on vascular biology, this drug has toxic effects significantly less severe than 5-FU and cardiotoxicity is an uncommon adverse effect. Other possible mechanisms include endothelial dysfunction with thrombosis, direct damage of myocytes and hypersensitivity reaction with Kounis syndrome [70]. Interestingly, 5-FU is able to inhibit angiogenesis by suppressing the stimulating effect of vascular endothelial growth factor (VEGF) on the synthesis of DNA during endothelial cells (EC) mitosis [71]. In addition, it determines endothelial damage with a ROS-dependent mechanism [72]. Although the inhibition of EC proliferation during tumor angiogenesis is an important strategy for tumor

Table 1
Vascular toxicity induced by main chemotherapeutics.

Anticancer treatment	Vascular toxic effect	Mechanism
Anthracyclines	Negative arterial remodeling	ROS, drug-accumulation in nuclei, mitochondria, DNA repair, sarcoplasmic reticulum stress, nitrosative stress, the activity on drug transporters (including MDR1 and MRP1), drug metabolism, TopI and II inhibition
5-Fluorouracil	Myocardial ischemia	Vasospasm (hypothesized cause) ROS
Cisplatin	Myocardial ischemia	Cytotoxicity in endothelial cells with increased formation of pro-coagulant endothelial micro-particles and free radicals

starvation, thus blocking their progression, systemic inhibition of VEGF also hampers endothelial cell homeostasis leading to atherogenesis and arterial thromboembolic events, which often results in myocardial infarction, cerebrovascular insults, and peripheral or mesenteric ischemia [73–75].

Taxanes are microtubule-binding drugs, whose main mechanism of action involves the inhibition of cell division, chromatid separation and growth, ultimately leading to cell death. As with various cancer cells, taxanes affect the basic functions also of ECs, such as proliferation and invasion [76]. Moreover, the taxane paclitaxel is also able to enhance endothelial tissue factor (TF) expression through its stabilizing effect on microtubules and activation of c-jun kinase (JNK), with thrombomodulin down regulating and increased protein nitration [77]. *Vincristine*, another tubulin blocker, can adversely affect cardiac microvascular ECs in rats [78].

Other classical chemotherapeutics, including *cyclophosphamide* (a nitrogen mustard inducing DNA alkylation [79]), *bleomycin* (*anti*-tumor antibiotic that induces DNA degradation) and vinca alkaloids (depolarizing agents causing spiral-like distortions of the cellular microtubules [80]) have been considered responsible for the endothelial damage.

6. Vascular damage caused by radiotherapy

Vascular toxicity can also be caused by radiotherapy. This therapeutic approach produces a wide range of deleterious effects on the heart including pericarditis, coronary artery disease (CAD), myocardial infarction, valvular heart disease, rhythm abnormalities, no ischemic myocardial and damage to the conduction system. The risk of cardiovascular toxicity is increased in the presence of the following conditions: anterior or left chest irradiation, high cumulative dose of radiation (>30 Gy), young age (<50 years), high dose of radiation fraction (>2 Gy/day), concomitant chemotherapy, cardiovascular risk factors and pre-existing cardiovascular diseases [81]. Radiotherapy can cause the valve apparatus and thickening of the leaflet, valvular fibrosis, shortening and calcification, stenotic aortic lesions, accelerated CAD involving coronary ostia and proximal segments. Radiotherapy induces extensive lesions, involving long segments and atypical areas of the carotid arteries. In Hodgkin's lymphoma, the estimated incidence of vascular lesions (including the subclavian artery stenosis) is about 7.4%. Radiotherapy can also cause calcification of the ascending aorta and aortic arch and other vascular lesions inside the radiation field (Table 2) [63] and can induce the formation of atherosclerotic lesions causing narrowing or occlusion of the vessel. From a microscopic point of view, these lesions are comparable to those that are not connected to radiotherapy. The induction of the atherogenic process seems to be accelerated in patients with hypercholesterolemia. The vascular damage induced by irradiation involves the endothelial cells, the ground substance, elastic lamina, smooth muscle cells and lysosomal activation. Once these elements are impaired, the permeability to circulating lipids increases. Furthermore, there is the

Table 2
Vascular toxic effects induced by radiotherapy.

Anticancer treatment	Vascular toxic effect
Radiotherapy	Stenotic aortic lesion Accelerated coronary artery disease with involving of coronary ostia and proximal segments Carotid lesion Calcification of the ascending aorta and aortic arch Lesions of any other vascular segments present within the radiation field

elastic tissue capability to recover from damage, which determines the formation of a plaque constituted by fibrosis, including the periarterial fibrosis, fatty infiltration and the heap of macrophage-derived foam cells, demolition of the intima and calcification. So, the irradiated arteries show lesions characterized by macrophage-rich nuclei, low collagen content, and intraplaque hemorrhage. These elements represent a strong atherogenic stimulus, that leads to the formation of a vulnerable plaque. As regards the idiopathic atherogenesis, ROS have a role in the atherogenic process induced by radiations. In fact, the radiolytic hydrolysis stimulates the production of different types of ROS, including superoxide anion (O_2^-) (the major product in the presence of oxygen), hydrogen peroxide (H_2O_2) and hydroxyl radical (HO•). Furthermore radiation promotes inflammation and thrombosis, supporting ROS production, alterations in endothelial cells and, consequently, vascular damage. It should be noted that together with changes in the endothelial cells, radiation also determines the death of endothelial cells and the resulting exposure of subendothelial thrombotic factors, thereby facilitating vulnerable plaque rupture and thrombotic events (Fig. 1) [82–84]. In addition, the presence of cardiovascular risk factors (e.g., smoking and dyslipidemia) may increase the risk of cardiotoxicity after radiotherapy [85].

7. Detection and monitoring of vascular toxicity

Since cancer therapies can cause vascular damage through various mechanisms, it is reasonable to assess vascular function in cancer patients treated with these drugs. Endothelial dysfunction is an early step towards more advanced vascular damage and atherothrombotic events. Some evidence supports the utility of non-invasive assessment

Table 3
Vascular toxic effects induced by target therapy.

Anticancer treatment	Vascular toxic effect	Target
Bevacizumab	Arterial hypertension myocardial ischemia, atherothrombotic events (ATEs)	VEGF-A
Sunitinib	Arterial hypertension	VEGFR1–3, PDGFR/, c-Kit, FMS-like tyrosine kinase-3 (FLT3), CSF-1R), RET
Pazopanib	Arterial hypertension	PDGFR, VEGFR, c-KIT.
Sorafenib	Arterial hypertension myocardial ischemia	VEGFR, PDGFR, Raf–1/B-Raf, c-Kit, FLT3
Regorafenib	Arterial hypertension myocardial ischemia	VEGFR 2–3, RET, KIT, PDGFR, RAF.
Axitinib	Arterial hypertension myocardial infarction	VEGFR
Cabozantinib	Venous thrombosis and rarely arterial thrombosis (myocardial infarction and stroke)	VEGF, MET, RET, KIT, Flt-3, AXL and Tie-2
Nilotinib	Accelerated atherosclerosis, peripheral arterial occlusive disease (PAOD), QTc prolongation.	Bcr-Abl, PDGF, cKit, BCR-ABL, PDGFR, c-KIT, CSF-1R, DDR1
Ponatinib	Arterial hypertension, cardiovascular events.	Bcr-Abl T315I, Src SFKs, Src e Lyn.
Dasatinib	Pleural effusion, heart failure, pulmonary hypertension.	BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ.

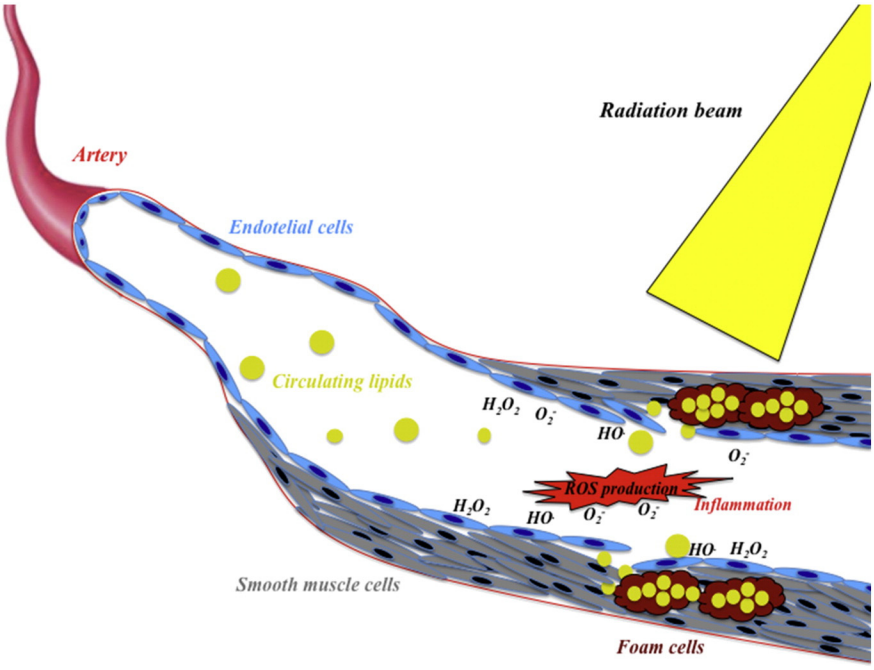

Fig. 1. Vascular damage caused by radiotherapy. Legend: ROS, reactive oxygen species.

of flow-mediated dilation (FMD = flow hyperemic mediated dilation) of the brachial artery to detect endothelial dysfunction. This technique involves measurement of the vessel diameter of the brachial artery at baseline and after a minute of hyperemic flow, at the peak of mediated vasodilation by shear stress. Vasodilatation is impaired in case of endothelial dysfunction.

Increased intima-media thickness of the common carotid artery, measured by ultrasound scan, is a well-known early marker of atherosclerosis, which significantly correlates with the development of cardiovascular diseases [86,87].

Therefore, carotid ultrasound scan is an easy and inexpensive test that can be used routinely to assess the onset of atherosclerosis and to stratify cardiovascular risk especially in intermediate-risk patients.

More recently, great emphasis has been placed on the role of arterial stiffness (AS) in the identification of vascular changes in sub-clinical, asymptomatic stages. In fact, the increase in stiffness is a very early sign of vascular damage, earlier than intima media thickening. Moreover, it has already been shown that the PWV is a strong predictor of overall mortality and cardiovascular events (CE) in both general populations and hypertensive patients, and that PWV assessment significantly improves the risk stratification [88]. In clinical practice, there are three different methods to measure AS: carotid-femoral (cf) PWV, central pulse wave analysis and local arterial stiffness. The cf-PWV is considered as the gold-standard measurement of AS, especially because it is simple to obtain and because multiple epidemiologic studies have demonstrated its predictive value for CE. The main limitation of PWV interpretation is that it is significantly affected by high blood pressure (BP) [89]. Central pulse-wave analysis provides additional information on wave reflections. Local AS can be easily measured on the carotid arteries with ultrasound devices. Echo-tracking devices have been developed to measure end-diastolic diameters and change in diameter with a very high precision [75]. Local AS can also be evaluated with magnetic resonance imaging (MRI), but this methodology requires expensive equipment and a high level of technical expertise. In addition it is not easily performed in routine settings [90]. Regional AS can be evaluated with different devices and methods, such as mechanotransducers, tonometers, Doppler probes, and echo tracking.

Previous studies assessing cf-PWV and augmentation index have shown that anti-VEGFR treatment is associated with a marked increase in both brachial and central BP and early aortic reversible stiffening [91]. Specifically, BP (blood pressure) and cf-PWV, systolic (global longitudinal strain) and diastolic function have been shown to change in patients after the initiation of the anti-VEGFR treatment. Interestingly, changes in BP and stiffness seemed to be reversible upon discontinuation of treatment, while LV systolic and diastolic functions were persistently abnormal [92].

Arterial stiffness was also increased in patients treated with anthracyclines. A significant increase in aortic stiffness was observed after 4 months of exposure to anthracyclines [93]. In addition, in childhood cancer survivors treated with chemotherapy, AS was increased compared with patients without cancer [94].

Thus, AS evaluation could be used for early detection of vascular damage induced by conventional and new antineoplastic drugs and to accurately stratify CV risk in cancer patients. However, further studies are needed to determine its true predictive value and usefulness as a screening tool in this specific clinical scenario.

8. Strategies to prevent and treat vascular toxicity

Antineoplastic drugs can not only cause cardiac dysfunction but also vascular injury. Given the high incidence of arterial hypertension induced by VEGF/VEGFR inhibitors, it is very important to control BP before starting any treatment and accurately monitor its variations during the course of therapy. It is also mandatory for the control of cardiovascular risk factors such as diabetes mellitus and dyslipidemia, which can make patients more prone to vascular injury. Recently, the importance of monitoring cardiac function by echocardiography, which is actually recommended after 1 month since starting VEGF or VEGFR inhibitors and then every 3 months [81], has been emphasized [95]. On the contrary, there are no standardized guidelines regarding the monitoring of vascular complications, especially in patients treated with VEGF/VEGFR inhibitors who are more prone.

We believe that not only cardiac but also vascular function should be evaluated in cancer patients. An ultrasound of the carotid arteries is probably the most simple test to perform in routine practice and could be useful to guide the clinician towards a more efficient management of cardiovascular risk factors. However, as local AS gives earlier information and is therefore worth to be measured, when possible. This

approach could reasonably be recommended in patients with risk factors, together with a thorough echocardiographic assessment. The optimal management of hypertension caused by VEGFR inhibitors remains controversial, although several potential therapeutic approaches have been hypothesized [96]. In the absence of specific data, favorite antihypertensive agents for the treatment of hypertension in these patients are ACE-I (angiotensin-converting-enzyme inhibitor) and beta-blockers, because of their well-known cardioprotective effects, although there are minimal data suggesting superiority of a single class of agents. Given the hypothesized role for decreased NO signaling in the pathogenesis of hypertension with these agents, nitrates can be a relevant mechanistic class of drugs to be used. In addition, nebivolol can enhance NO signaling, suggesting its therapeutic potential in this population [97]. Early and aggressive onset of antihypertensive therapy appears to help the maintenance of the treatment program and to reduce the risk of major complications, including malignant hypertension and reversible posterior leukencephalopathy. In patients treated with VEGF-VEGFR inhibitors it has been recently recommend to: (1) carry out a formal risk assessment for existing cardiovascular disease and potential cardiovascular complications before treatment, recognizing that pre-existing hypertension and cardiovascular disease are common in patients with cancer, (2) actively monitor BP elevations and cardiac toxicity with more frequent assessments during the first treatment cycle, and (3) aggressively manage BP elevations and early symptoms and signs of cardiac toxicity to prevent complications of antiangiogenic drugs [98,99].

9. Conclusions and future directions

Radiotherapy, chemotherapy and target therapies can cause not only cardiac toxicity but also the vascular toxicity. It is also well known that because of ventricular-arterial coupling, ventricular and arterial function is a continuum [100]. Therefore, an overall assessment of both cardiac and vascular functions, is crucial for cancer patients, to avoid late complications.

In particular, GLS and PWV measures may add important information in the early identification of subclinical cardiovascular damage, in order to promptly initiate any protective treatments and to prevent future overt damage.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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