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Cardiovascular Complications in Cancer Therapy

Humana Press

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Abbreviations

3DE	Three-dimensional echocardiography
3D-STE	Three-dimensional speckle tracking echocardiography
5-FU	5-Fluorouracil
ABI	Ankle-brachial index
ACEi	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndromes
AF	Atrial fibrillation
AHA	American Heart Association
AMI	Acute myocardial infarction
AMPK	Adenosine monophosphate-activated protein kinase
AP/BP	Accelerated phase/blast phase
ARBs	Angiotensin receptor blockers
AS	Arterial stiffness
ASCO	American Society of Clinical Oncology
ASE	American Society of Echocardiography
ATEs	Atherothrombotic events
AV	Aortic valve
BMT	Bone marrow transplantation
BNP	B-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCB	Calcium channel blockers
CDK(s)	Cyclin-dependent kinase(s)
CHF	Congestive heart failure
CML	Chronic myeloid leukaemia
CMR	Cardiac [cardiovascular] magnetic resonance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTRCD	Cancer therapeutics-related cardiac dysfunction
CTX	Cardiotoxicity
CUS	Compression ultrasonography
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factors

DBP	Diastolic blood pressure
DM	Diabetes mellitus
DOAC(s)	Direct oral anticoagulant(s)
DVT	Deep vein thrombosis
EACVI	European Association of Cardiovascular Imaging
EBCT	Electron beam computed tomography
ECG	Electrocardiography
ECs	Endothelial cells
EF	Ejection fraction
eNOS	Endothelial nitric oxide synthase
EPO	Erythropoietin
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FMD	Flow-mediated dilation
FRS	FRAMINGHAM Risk Score
Gal-3	*Galectin-3*
GIST	Gastrointestinal stromal tumour
GLS	Global longitudinal strain
GPBB	Glycogen phosphorylase BB
HER2	Human epidermal growth factor receptor 2
HF	Heart failure
H-FABP	Heart-type fatty acid-binding protein
IMRT	Intensity-modulated radiotherapy
IMT	Intima-media thickness
JNC	Joint National Committee
LA	Left atrium
LMWH	Low-molecular-weight heparin
LQRS	Long QT syndrome
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MR	Molecular response
MUGA	Radionuclide angiography
MV	Mitral valve
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NO	Nitrous oxide/nitrogen monoxide
NOAC	New oral anticoagulants
PAD	Peripheral artery disease
PAH	Pulmonary arterial hypertension
PBI	Partial breast irradiation
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PH	Pulmonary hypertension
PRO	Patient-reported outcome
PT	Proton beam therapy
PVOD	Pulmonary veno-occlusive disease
PWV	Pulse wave velocity

QTc	QT prolongation
RA	Right atrium
RAAS	Renin-angiotensin-aldosterone system
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RIHD	Radiation-induced heart damage
ROS	Reactive oxygen species
RR	Relative risk
RV	Right ventricle
SBP	Systolic blood pressure
SNPs	Single nucleotide polymorphisms
SPECT	Single-photon emission computed tomography
STE	Speckle tracking echocardiography
TAVI	Transcatheter aortic valve implantation
TDI	Tissue Doppler imaging
TdP	*Torsades de pointes*
TF	Tissue factor
TKI	Tyrosine kinase inhibitor
TNF	Tumour necrosis factor
TnI	Troponin I
VDA(s)	Vascular disrupting agent(s)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHD	Valvular heart disease
VKA	Vitamin K antagonists
VTA(s)	Vascular targeting agent(s)
VTE	Venous thromboembolism

Introduction

1

Antonio Russo, Giuseppina Novo, Patrizio Lancellotti, Fausto J. Pinto, and Antonio Giordano

Thanks to more and more effective antineoplastic treatments, among them target therapies and immunotherapy, and the advances in early diagnosis of tumors, the life expectancy of patients suffering from cancer has significantly increased in the last 5 years [1, 2]. The increase in survival has created a population of patients "long survivors" with chronic cancer disease who are more exposed to develop complications of antineoplastic treatments [3].

Cardiovascular complications are among the most serious ones and may lead not only to heart failure, that could be severe, but also to ischemic heart disease, peripheral arterial disease and stroke, cardiac arrhythmias, valves disease and pericardial disease, venous thromboembolism, arterial hypertension, and pulmonary hypertension [4].

Moreover tumor and cardiovascular diseases often share the same risk factors. This increases the probability for these conditions to coexist in the same patient [5].

On these premises, a new branch of cardiology, cardio-oncology, was born, aiming to prevent and early diagnose and manage cardiac damage caused by the use of old and new antineoplastic drugs and to facilitate the cancer treatment and to avoid its suspension. Cardio-oncology is based on the cooperation between cardiologists and oncologists and possibly other related specialists aimed to a collegial and more efficient management of the oncological patient, to provide optimal care but also for the related socioeconomic implications. Given the awareness of the cardiological complications related to anticancer treatment, it is now necessary to spread the cardio-oncology knowledge.

With this aim it is born the idea of publishing this book, addressed to cardiologists, oncologists, and other specialists who are facing oncological patients. The authors of this book are cardiologists and oncologists, involved in their daily practice with oncological patients, most of them are expert, known all over the world, for their scientific publications in this field.

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In this book we will review the pathophysiological mechanisms leading to cardiovascular toxicity related to the various antineoplastic drugs, we will focus on the main cardiological complications that may occur, and we will discuss the diagnostic modalities to detect earlier as possible these and the actual preventive and therapeutic strategies.

This book offers a practical landmark to increase the awareness on cardio-oncology and to help each clinician on his/her everyday practice. In fact nowadays it is more and more common to deal with oncological patients who develop heart disease and who require a specific management. On the other hand in our daily practice we often have to evaluate the suitability of a given patient to start a certain oncological treatment, potentially cardiotoxic but possibly lifesaving, and we cannot refrain ourselves from knowing the possible risks for the heart and the vessels and the strategies to be implemented to minimize them.

In addition to the book, we are aware that it is necessary to increase the culture of cardio-oncology with specific training course and scientific events and to develop new efficient and sustainable diagnostic and therapeutic paths to address these issues, involving a multidisciplinary team of experts and creating cardio-oncology units that are already a virtuous reality in some center.

Unfortunately we are aware that despite a growing number of scientific papers have been recently produced about cardio-oncology, the level of evidence to develop guidelines is still lacking, and the recommendations provided in this book largely represent the opinions of experts. For this reason large and prospective studies to evaluate the burden of antineoplastic treatment-related toxicity and to settle the management of such patients are needed, in order to increase the levels of evidence and to develop cardio-oncology guidelines.

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2 Mechanisms of Cardiovascular Damage Induced by Traditional Chemotherapy

Valentina Mercurio, Giulio Agnetti, Pasquale Pagliaro, and Carlo G. Tocchetti

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

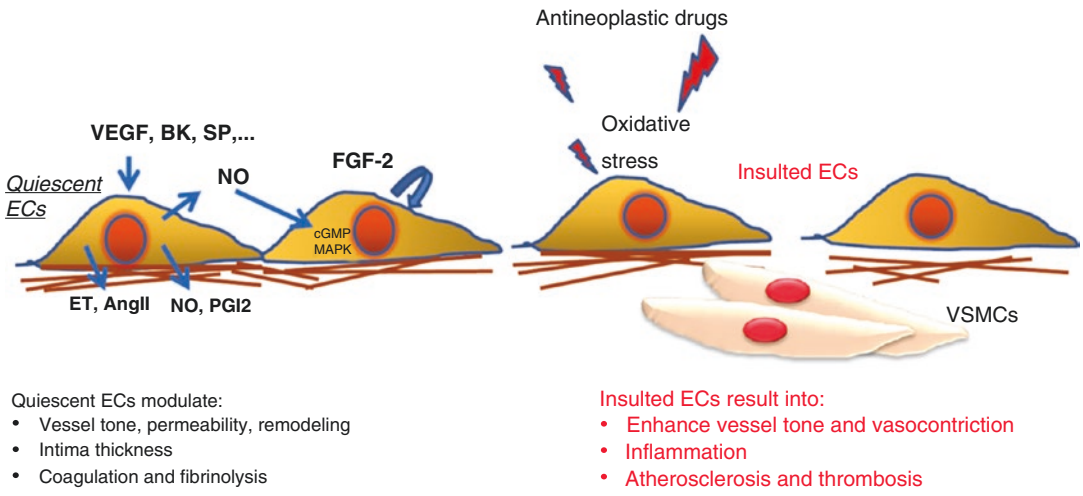

Fig. 2.1 Damages induced by anticancer drugs on endothelial cells. AngII angiotensin II, BK bradykinin, cGMP cyclic guanosine monophosphate, ET endothelin, FGF2 fibroblast growth factor, MAPK mitogen-activated proteine kinase, NO nitric oxide, PGI2 prostacyclin, SP substance P, VEGF vascular endothelial 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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3 Molecular Mechanisms of Cardiovascular Damage Induced by Anti-HER-2 Therapies

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Introduction

In order to overcome the increased risk of cardiovascular toxicity associated with classic chemotherapeutics, since the last two decades, newer biological drugs have been designed to "target" specific proteins involved in cancer proliferation. Unfortunately, these proteins are also important for the maintenance of cardiovascular homeostasis. Endothelial damage is a common feature not only of anti-VEGF agents (bevacizumab, sunitinib, sorafenib) but also of anti-Her-2 drugs [1, 2]. The humanized anti-ErbB2 antibody trastuzumab is the prototypical biological drug first introduced in antineoplastic protocols for the treatment of ErbB2+ breast cancer. ErbB2 is a transmembrane glycoprotein receptor overexpressed in several breast cancers, which also plays a major role in the heart in cell growth, including myocyte growth, and inhibition of apoptosis [3–7]. When administered alone, the risk of significant cardiotoxicity by anti-Her-2 drugs appears to be low, but in clinical trials, 25% of patients treated with trastuzumab developed systolic dysfunction, especially when administered with or shortly after doxorubicin [2, 8–10].

Cardiac Toxicity of Anti-ErbB2 Inhibitors

Inhibition of the axis neuregulin 1/ErbB2 signaling has been considered the key cardiotoxic effect of anti-ErbB2 drugs [11, 12]. Briefly, adult cardiac microvascular endothelial cells can release neuregulin 1 (NRG1, especially the NRG1b isoform) [13] following to various stimuli, including mechanical strain. NRG1 acts on cardiac myocytes in a paracrine manner, triggering ErbB4/ErbB4 homodimerization and ErbB4/ErbB2 heterodimerization to induce protective pathways in response to stress [11, 12]. Importantly, the ErbB2 pathway regulates cell survival and function and can even impact mammalian heart regeneration [14] and can be stimulated when the heart faces adverse hemodynamics or other stress, such as ANT therapies (Fig. 3.1) [11, 15]. It has been hypothesized that anti-ErbB2 drugs can induce myocyte damage and,

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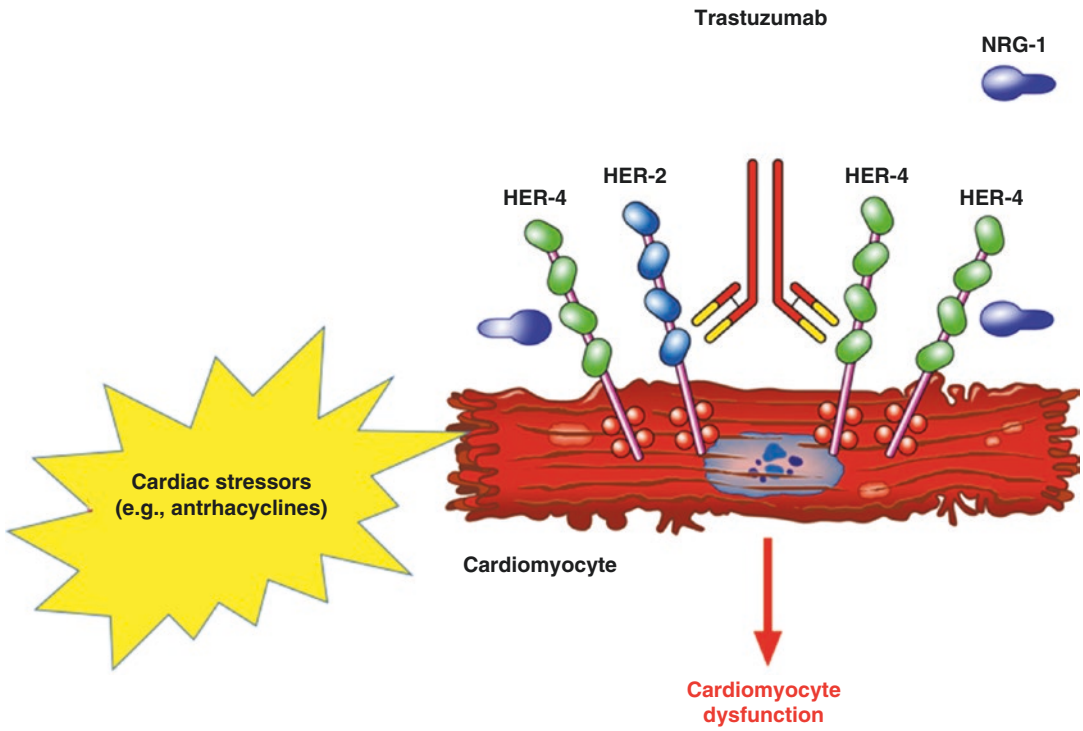

Fig. 3.1 Cardiomyocyte damage induced by trastuzumab. Cardiac stressors, such as pressure or volume overload but also anthracyclines, are able to upregulate Her-2 on cardiomyocyte, rendering these cells more susceptible to following exposure to trastuzumab

eventually, HF by deranging the NRG1/ErbB4/ErbB2 pathway in the myocardium. This event is more likely to occur upon cardiomyocyte exposure to other stressors, such as hypertension or doxorubicin [11, 16, 17]. Such concept seems to be corroborated by seminal papers that showed LV dilation in ErbB2 cardiac KO mice, with enhanced susceptibility to cardiomyocyte damage from anthracyclines [18, 19]. On the opposite, ErbB2-overexpressor hearts exhibited reduced levels of ROS in mitochondria, with lower ROS levels and less cell death in neonatal myocytes isolated from ErbB2(tg) hearts after administration of anthracyclines. This was due to higher levels of glutathione peroxidase 1 (GPx1) protein and activity, coupled to an increase of two known GPx activators, c-Abl and Arg, suggesting novel mechanisms by which ErbB2 blockers can damage heart structure and function [20].

Additional studies on NRG1/ErbB4/ErbB2 have moved from cancer and HF to heart disease from any cause, paving the way to novel therapeutic implications. For instance, in mice subjected to pressure overload, both mRNA and protein levels of ErbB4 and ErbB2 were significantly diminished with the progression of the disease from hypertrophy to decompensated HF [7, 11, 21]. Consistently, human failing myocardia exhibited lower ErbB2 and ErbB4 receptor expression and activation/phosphorylation, when compared to organ donors [22]. Interestingly, levels of ErbB4 and ErbB2 could be restored back to normal by implanting LV assist device and unloading the heart [22, 23]. In an apparent contrast with these results, there was enhanced phosphorylation of ErbB4 and ErbB2 in dogs with HF induced by tachypacing [24]. Dysregulation of the intracellular downstream effectors of ErbB4 and ErbB2, ERK1/2, and Akt was also observed, suggesting deranged NRG1/ErbB4/ErbB2 pathway. Importantly, most studies show enhanced expression of NRG1 in HF compared to control conditions [11, 22, 24]. This evidence points out that in the pathophysiology of

HF, a major player is deregulation of the NRG1/ErbB4/ErbB2 signaling. In particular, anti-ERbB2 drugs can bring to cardiac dysfunction; and, in spite of normal or enhanced levels of NRG1, ErbB4/ErbB2 is downregulated and/or uncoupled from intracellular signaling, possibly exacerbating LV decompensation [11]. In addition, recent studies show that catecholamines, which usually increase in the setting of heart dysfunction and with administration of doxorubicin [11, 25, 26], can enhance ErbB2 expression in cardiomyocytes, thus making these cells more vulnerable to the effects of trastuzumab, bringing to cardiotoxicity [27].

Vascular Toxicity of Anti-ErbB2 Inhibitors

ErbB2 inhibition was also demonstrated to cause damage to vascular function through a reduction in NO bioavailability and an increase in ROS production [28, 29]. Indeed, cardiac endothelium produces the growth factor NRG1, which activates the Her-2/Her-4 complex, thus activating cascades of ERK–MAPK and PI3K–Akt signaling pathways, promoting cell survival [13]. Importantly, NRG1 modulates angiogenesis and NOS-dependent desensitization of adrenergic stimulation [30]. Trastuzumab treatment acts on Her-2, inhibiting survival signals and bringing to mitochondrial dysfunction and depletion of energy supplies. In addition, stress factors, such as hypertension or previous anthracycline administration, increase the production of reactive oxygen species (ROS) [31].

Under normal conditions, cells restrict this event by overexpressing Her-2, thus leading to the activation of the cell survival pathways. Her-2 blockade does not allow the activation of these pathways, thus creating a state of enhanced oxidative stress leading to apoptosis [3–6, 8, 30, 32–35].

Importantly, an inverse correlation between circulating levels of neuregulin 1 and level of coronary artery disease has been observed [36]. In addition, low NRG1 synthesis impairs cardiac recovery after an ischemic insult, and impairment in NRG1/HER axis was found in experimental diabetic cardiomyopathy [37, 38]. Intriguingly, patients with coronary artery disease and those with diabetes mellitus also have a higher risk of doxorubicin-induced cardiomyopathy, and neuregulin administration ameliorates heart function after anthracycline-induced myocardial injury [39]. Hence, there may be elements of neuregulin-related endothelial–myocardial coupling even in mechanisms of toxicity from classic cardiotoxic drugs such as anthracyclines. Accordingly, it can be postulated that patients with higher activity/stimulation of the NRG1/HER signaling pathway are more susceptible to trastuzumab cardiotoxicity. This would explain the increased incidence of cardiotoxicity in patients treated with trastuzumab in close temporal proximity to anthracyclines. The fact that subjects with concomitant cardiovascular risk factors or disease have an increased higher risk suggests that this pathway is particularly important and any further reduction from baseline can be detrimental. Experimental work has shown that lack of ErbB2 induces the development of dilated cardiomyopathy and impaired adaptation response to after load increase [18]. Further studies will need to demonstrate correlations between ErbB2 regulation of cardiac function and microvascular density [40].

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Cardiovascular Damage Induced by Radiotherapy

4

Antonio Galvano, Giuseppina Novo, Mario Roselli, Antonio Giordano, and Antonio Russo

Introduction

Improvements in the management of cancer patients have allowed an increase in the number of patients defined as long survivors [1]. A longer survival, however, is responsible for a higher percentage of long-term cardiovascular side effects, including those related to radiotherapy.

Radiotherapy in the oncological field has been experimented since the early 1900s, leading in patients with Hodgkin's lymphomas to a strong improvement in the 5-year survival rate of about 15% [2]. Together with survival, authors also reported an increase in the incidence of radiotherapy-related heart disease that has become one of the leading causes of death [3]. This phenomenon is mainly related to the amount of radiation given to the heart. Cardiovascular risk factors, such as hypertension, dyslipidaemia, diabetes mellitus and sedentary lifestyle and concomitant cardiac disease, may favour cardiotoxicity. The reason why radiotherapy may induce cardiac damage is not completely understood; it may possibly be due to a persistent inflammatory response or to a genetic predisposition [4, 5]. Few years ago some experience have studied the association between cardiovascular damage and radiotherapy treatments administered to patients with Hodgkin's lymphoma and breast cancer. In the first case, the study showed that the use of conventional mediastinal radiotherapy, not including the modern techniques available today, was responsible for an increased risk of myocardial infarction ranging from 1.5 to 3 times compared to those who did not undergo mediastinal radiotherapy. In particular, one of these studies showed that a greater than 30 Gy radiation dose was subject to an increased risk of cardiovascular damage [6, 7].

Concerning breast cancer, a meta-analysis of eight randomized studies has shown that radiotherapy in this patient setting was responsible for an increase of more than 60% in cardiovascular mortality. Other studies underlined that more than

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half of these asymptomatic patients developed cardiogenic damage within the first 6 months after the end of radiotherapy [8, 9]. Today the use of modern conformational 3D radiotherapy and intensity-modulated radiotherapy (IMRT) has contributed to reduce the risk of cardiovascular damage from radiotherapy. A recent population-based case-control study that analysed radiotherapy vascular damage in patients with breast cancer treated from around 1960 and at the beginning of the 2000s showed a small increase in the incidence of cardiac ischemic disease, balanced by a significant increase in long-lived patients [10]. Despite these technological advances, radiotherapy-induced heart damage (RIHD) remains a matter of enormous clinical relevance, since it produces symptomatic cardiovascular disease in about 10% of those who undergo radiotherapy [11].

Radiotherapy can induce vascular damage leading to accelerated atherosclerosis but also myocardial damage that can involve all the heart's layers leading to valvular damage, cardiomyopathy and pericarditis.

Mechanisms of Radiotherapy-induced Cardiac Damage

First data regarding radiation-related damage have been recorded studying long survivors after Hiroshima and Nagasaki disasters. Scientists have computed an average dose of radiation ranging from 0 to 3 Gy for 50 years resulting in a 10% of cardiovascular mortality [12]. Since cardiomyocytes are very resistant to RIHD due to their postmitotic state, injuries are mainly attributable to the involvement of endothelial cells. Chronic inflammations can be considered the fundamental moment of RIHD. This leads to endothelial dysfunction and accumulation of many inflammatory cells such as macrophages, able to release many pro-inflammatory cytokines including TNF and some interleukins (IL-1, IL-6, IL-8). These processes favour the penetration of lipids into the vascular wall and lead to the formation of atherosclerotic plaques [13–16].

Moreover, irradiated endothelial cells trigger some molecules such as intracellular adhesion molecule (ICAM)-1 and platelet endothelial cell adhesion molecule (PECAM)-1 that are responsible for the leukocyte aggregation. The appearance of fibrosis will also be facilitated by the production of other cytokines such as plasminogen activators inhibitor thrombomodulin, which make endothelial cells prothrombotic and atherogenic [17–19].

Regarding valve injury, radiation would seem to activate some fibrogenic growth factors among which there are the tissue growth factor beta-1 and myofibroblasts and could also stimulate collagen synthesis at systemic level. Aortic valvular irradiation on interstitial cells would induce the expression of some critical bone proteins such as alkaline phosphatase, osteopontin, bone morphogenic protein 2 and Runx2 that could somehow explain the occurrence of radiotherapy-related valve calcification [20, 21]. Today radiotherapy represents a cornerstone in the treatment of neoplasms due to its ability to cause direct DNA damage. Oncology trials have led to better understand the relationship between radiotherapy and vascular damage, and numerous experiences have shown that patients affected by thoracic neoplasms such as Hodgkin's lymphoma, breast cancer, oesophagus cancer or lung cancer are more exposed to cardiovascular system failure even after 10 or 30 years from exposure to radiotherapy [22]. In addition to the site of cancer to be irradiated (higher risk for tumour close to heart tissue), there are other clinical risk factors associated with RIHD as anterior or left radiotherapy, radiotherapy doses higher than 30 Gy, age less than 50 years, daily radiation >2 Gy, inadequate or absent shielding, concomitant use of chemotherapy (e.g. anthracyclines), pre-existing cardiovascular disease, and the above-mentioned cardiovascular risk factors [23].

Pericardium affection pathophysiologic mechanism foresees that radiotherapy causes a microvascular damage that increases capillary permeability by producing an exudate rich in proteins and promote an inflammatory status.

RIHD could be related to microvascular insults that lead to ischemia and are responsible for replacing myocytes with interstizial fibrosis. [24]. In addition, irradiation results in

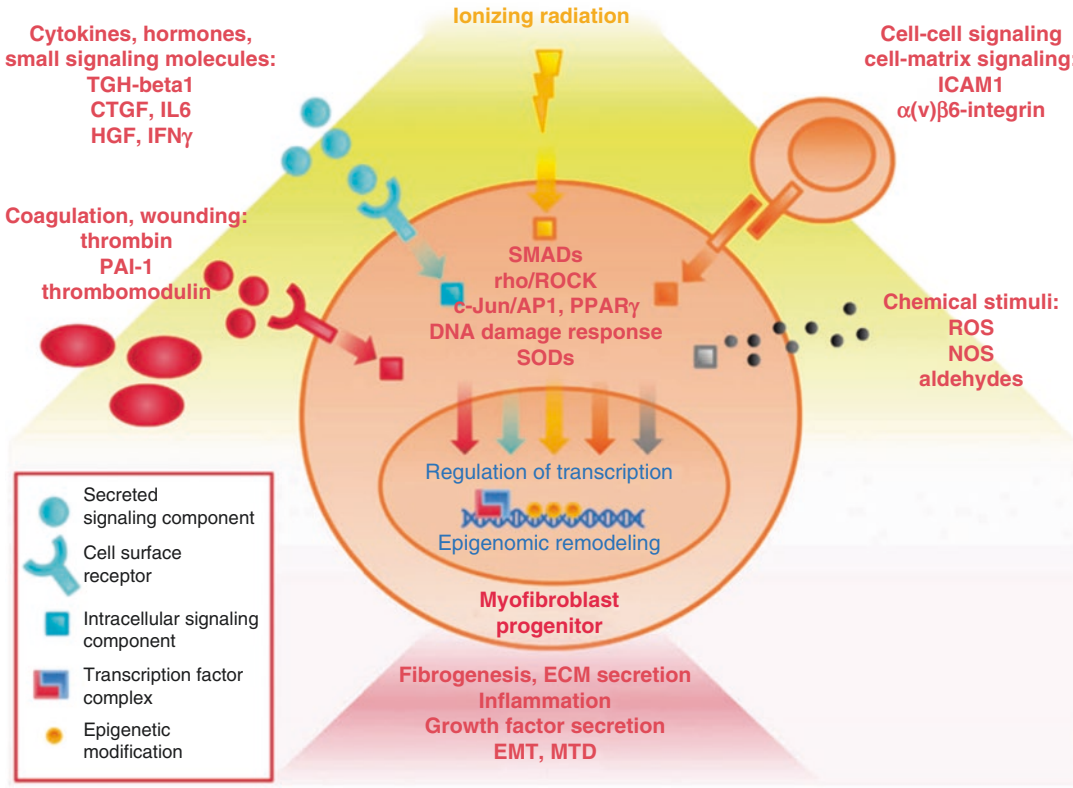

Fig. 4.1 Molecular mechanisms of ionizing radiation damage at tissue level. (From Taunk et al. [79])

increased production of collagen types I and III that may cause impairment of ventricular relaxation during the diastolic phase, as reported in an autopsy study [25].

The main aspects of the cardiac changes caused by radiotherapy in cancer patients receiving chemotherapy will be discussed below (Figs. 4.1 and 4.2).

Coronary Artery Disease (CAD)

Coronary artery disease (CAD) can usually develop within 20 years from the end of radiotherapy and generally tends to be asymptomatic. This process is accelerated by the development of atherosclerotic plaques in coronary vessels above all in proximal vessels and ostium [10, 26–29]. Atherosclerotic lesions caused by radiotherapy are morphologically identical to those not caused by radiotherapy and are characterized by accumulation of macrophages, plaque formation, and intimal proliferation [27]. In this special population, CAD can clinically appear with acute coronary syndrome, stable angina or even sudden cardiac death [28, 30].

Previous animal studies have shown in rabbits how a diet containing cholesterol can significantly increase the incidence of CAD due to radiotherapy, suggesting the possible role of cardiovascular risk factors in the genesis of damage [31]. A monocentric retrospective analysis evaluated patients affected by Hodgkin's lymphoma treated with radiotherapy showing that CAD occurred (approximately 10% after 20 years) in those patients who had at least one cardiovascular risk factor [32]. The modern imaging techniques have contributed to a better awareness of RI CAD showing, for example, that more than 40% of 114 asymptomatic breast cancer patients who underwent radiotherapy had an ischemia 24 months after the end of radiotherapy [33].

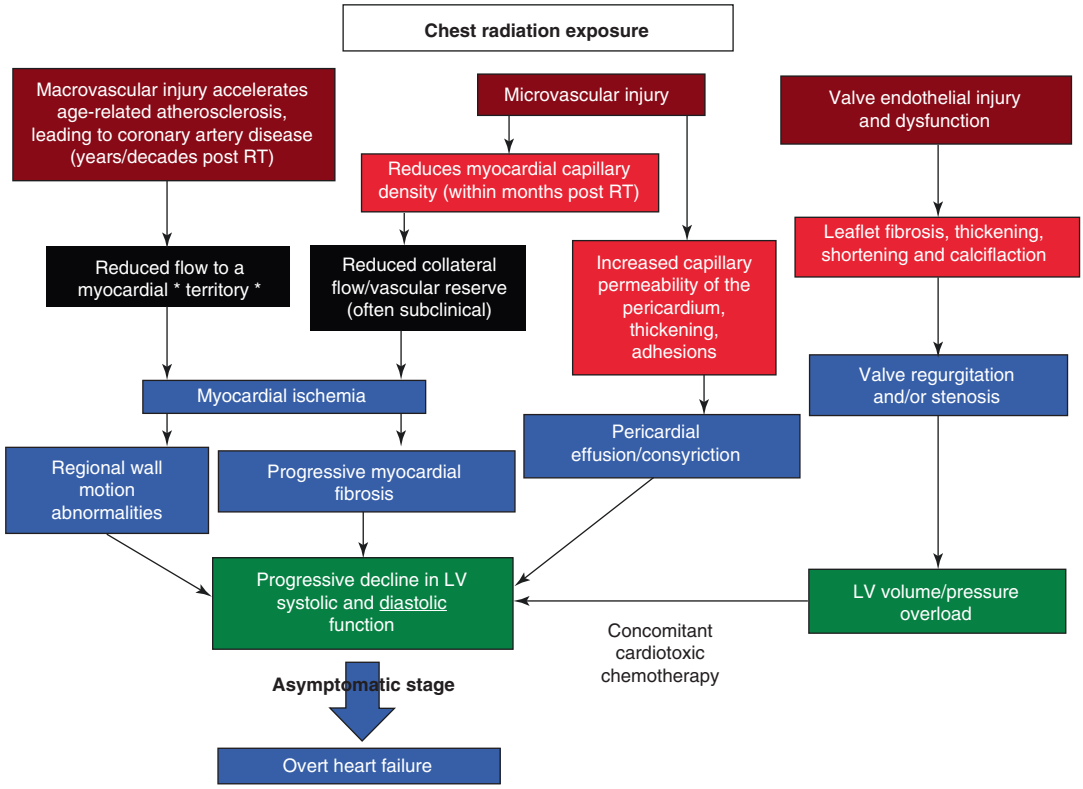

Fig. 4.2 Pathophysiology of RIHD. (From Lancellotti and Nkomo [80]. Reproduced with permission of Oxford University Press on behalf of the European Society of Cardiology)

In particular, a recent meta-analysis involving more than 20,000 breast cancer patients who received radiotherapy showed a significant annual CAD risk increase of about 27% compared to those who did not undergo radiotherapy [34]. This result goes in the same direction of other studies that pointed out that these asymptomatic perfusion defects could affect up to 20% of asymptomatic patients even more than 20 years after the end of treatment, suggesting a potential role of radiotherapy in giving a progressive damage that could be maintained over time [27].

Treatment of this condition is similar to that used in the general population and involves percutaneous interventions with stent placement or coronary artery bypass grafting, although the risk of restenosis and post-operative complications is still higher compared to patients not treated with radiotherapy [35, 36].

The percutaneous intervention, where possible, represents the most commonly practised option since the mediastinal fibrosis can make the surgical approach more complex and the irradiation often make the internal mammary artery not available for the graft [37]. Therefore, for patients undergoing bypass, a preliminary angiographic evaluation of the state of the internal mammary artery is advisable to ensure a successful outcome of the intervention [38].

Medical therapy is sometimes the only option, especially in patients with pulmonary fibrosis as a result of radiotherapy, which increases the risk of perioperative complications [39].

Pericardium

Pericardium involvement is a common RIHD damage. Some autoptic studies reported pericardial damage in approximately 70% of patients who underwent radiotherapy [24]. Pericardial RIHD include pericardial effusions (generally

asymptomatic, most common) and constrictive pericarditis that usually occur within a year [40]. Thanks to the improvement of radiation techniques today, the rate of clinically relevant pericardial manifestations is rather low, about 2.5% [41]. The occurrence can be clinically suggested by chest pain and fever; objectively pericardial rub can be listened. In more than 50% of cases, no medical treatment is required, although this condition is very sensitive to the use of steroids, diuretics, and rest [42]. Approximately 20% of patients who experience pericardial damage will manifest a chronic pericarditis in a period ranging from a few months to 2 to 5 years. Diagnosis of pericarditis is clinical and benefits from the use of the ECG, 2D echo and a chest X-ray. Contrast-enhanced CT or cardiac MR is useful to diagnose constrictive pericarditis.

Treatment of radio-induced pericarditis depends on the type and severity of the clinical condition that develops. Acute pericarditis, for example, is a non-frequent situation with early onset and a benign evolution which generally does not require a suspension of radiant treatment but which requires supportive treatment consisting of non-steroidal anti-inflammatories (more rarely steroids) and sometimes colchicine. With regard to late-onset forms, the most represented is the pericardial effusion that is generally asymptomatic. Sometimes pericardial effusion is clinically relevant giving dyspnoea or cardiac tamponade [43–45]. Tamponade is an emergency and must be relieved by needle pericardiocentesis. Pericardial effusion usually does need not to be drained unless there is tamponade. When pericardial effusion becomes chronic or recurrent, it may require pericardial window [44, 45].

Constrictive pericarditis is the more severe kind of pericarditis and usually may appear as a late complication of radiotherapy. Constrictive pericarditis is clinically associated with symptoms of congestive heart failure. Sometimes RIHD can also involve the myocardium, the valves, endocardium, and the coronary arteries, generating the state of pancarditis. Some studies have shown the unfavourable outcomes of patients who developed constrictive pericarditis and who were undergoing radiotherapy over those who did not undergo radiotherapy [46]. Constrictive pericarditis is managed as the first option with loop diuretics, although surgical pericardiectomy can be necessary, with more unfavourable results if compared to those patients who did not undergo radiotherapy treatment [47, 48].

Valves Disease

Radiotherapy doubles the risk of valve damage, although its incidence is not known (some studies reported a valve alteration in more than 80% of the cases analysed) [49, 50]. Generally, cusps and valves are affected by fibrotic phenomena and calcifications in the left side of the heart, probably due to the higher blood pressure and the consequent hemodynamic stress [21, 24, 51]. It is important to remember that the valvular RIHD is more frequent in the cardiac left side due to higher blood pressure exposure [52].

Typically, valve damage occurs after a long period, even 20 years, after the end of radiotherapy; it is more likely in patients who underwent a dose of radiotherapy greater than 30 Gy [52].

Clinically, about 70% of patients who undergo minor injury are asymptomatic. Valvular regurgitation is more frequent; sometimes it can be associated with stenosis [24, 52]. The thickness of the aortomitral curtain can be considered as a prognostic independent long-term mortality factor in these patients. Valvular RIHD is responsible for early (valvulitis) or chronic damage that is difficult to repair due to the high perioperative mortality rate compared to not radio-treated patients [53]. Mortality increases are directly proportional to the number of valves involved (1 valve 45% vs 13%; 2 or + valves 61% vs 17%). If a patient complains of symptoms suggestive of valve disease, 2D echo is advisable to identify early signs of thickening of the valvular flaps and of subvalve structures, regurgitation or stenosis. Cardiac MRI may refine diagnosis especially in a clinical research context.

Treatment is either valve repair or replacement, although the latter is the most used option (especially in severe aortic stenosis) being more feasible than repair due to the consequences of

radiotherapy [53, 54]. Valid and recent options for those who cannot undergo surgery, mainly due to severe mediastinal fibrosis, are the percutaneous mitral valve clips and the transcatheter aortic valve replacement; however today the available data are on small cohorts of patients [55].

Conduction System

Systemic cardiac anomalies manifest themselves after several years of radiotherapy, making it difficult to estimate the real incidence of this complication. Due to the nearness of the proximal portion of the beam with the endocardium, the right branch block represents one of the most common abnormalities due to mediastinal irradiation. The damage can be the direct result of irradiation or an indirect consequence of fibrosis and ischemia of adjacent tissues. Other less frequent abnormalities can be fascicular block or bifascicular block or atrioventricular block, this representing the most serious complication observed in patients undergoing mediastinal radiotherapy. Another frequent abnormalities is QT prolongation (QTc) reported in patients undergoing mediastinal radiotherapy during exercise, representing a negative prognostic factor.

The suspicion of conduction system injury is raised if a total dose of radiotherapy (>40 Gy) is used, the disturbance occurs after more than 10 years since treatment, and there is previous pericardial involvement or presence of other cardiac injuries or mediastinal involvement.

Dizziness, more rarely syncope and sometimes palpitations, shortness of breath, and chest discomfort are symptoms reported in this type of condition. The diagnosis is supported by some instrumental exams such as ECG and Holter monitoring. In patients suffering from complete or advanced atrioventricular block, pacemaker implantation is needed [56, 57].

Cardiomyopathy

Myocardial tissue can also be affected by mediastinal radiotherapy-induced damage, which generally appears 5 years after the end of the treatment.

Both the systolic and the diastolic phases can be impaired by mediastinal irradiation that may lead to dilatative or restrictive cardiomyopathy with an odds ratio of 1.9 in comparison to those patients who did not undergo procedure [22]. It should be noted that only 5% of patients reported a reduction in LVEF %, especially when radiotherapy was used in addition to protocols involving the use of chemotherapy associated with a high risk of cardiotoxicity (e.g. anthracycline) [58, 59]. Most patients affected by this condition do not have resting disorders but may experience symptoms during exercise. However, sometimes the condition can assume a remarkable clinical relevance, giving symptoms such as dyspnoea, fatigue and weakness, lower limbs oedema and sometimes even pulmonary oedema, especially when high doses of radiotherapy are delivered. The clinical suspicion requires an instrumental integration with the use of ECG, 2D echo and measurement of biomarkers.

The treatment of heart failure induced by radiotherapy does not differ from that used in the general population. It consists in the use of ACE inhibitors or angiotensin receptor blockers, beta-blockers and aldosterone antagonists. The lack of studies in this specific setting does not allow clear results about long-term mortality. Indeed, preclinical data on ACE inhibitors suggest that they are not able to protect from the late functional effects of radiotherapy. Heart transplantation may be an option to be considered in selected cases of end-stage heart failure, although radiotherapy is a negative prognostic factor for transplantation (5-year survival rate 58% vs 73%) [60, 61].

Carotid Artery Disease

Carotid arteries also may be affected by RIHD. Generally, carotid artery injury is asymptomatic, but, as described in some experiences, when the stenosis of the internal and common carotid artery is more than 70%, it could manifest symptomatically [62]. Specific risk factors for its pathogenesis have not yet been established. Some reports seem to associate cigarette smoking but sometimes with contradictory results [63]. Vascular involvement differs from the traditional

one because radiotherapy produces more extensive vascular damage involving less common areas and longer arterial segments [62].

Radiotherapy or chemo-radiotherapy combination regimens are valid options for the management of head and neck tumors, and therefore these patients are susceptible of vascular damage induced by radiotherapy. The risk is particularly high in the elderly [64, 65].

The diagnosis of carotid artery atherosclerosis is generally possible by ultrasound scan.

Patients must not be treated differently since population is not subjected to radiotherapy and may need surgery or percutaneous interventions especially in patients at high risk [62, 66].

Biomarkers

Humoral biomarkers (troponin or NT-pro BNP) are a potentially useful tool for early identification of chemotherapy-related cardiac damage. However there are still limits in the use of biomarkers due to the heterogeneity of the assays used, the uncertainty regarding the correct timing of measurement and cut-off. In fact actual studies reported results sometimes contradictory or not sufficiently robust to hesitate in recommendations to be transferred into clinical practice. According to some studies in patients exposed to high doses of anthracyclines, monitoring troponin I levels before and after each cycle of chemotherapy seems to be able to early predict myocardial damage. In particular, it seems that not only its increase has a prognostic value but also its negativity: in fact persistently not elevated troponin levels identified patients at low risk of experiencing adverse events at follow-up [67, 68]. Troponin I also demonstrated a potential role when used in patients undergoing combined radio-chemotherapy treatments as demonstrated in a series of 24 cancer patients (most with Hodgkin's lymphoma or breast cancer) in whom elevation of troponin I was able to predict subclinical myocardial damage undetectable with standard diagnostic technique. In another series of women with breast cancer treated with radiotherapy in addition to chemotherapy, however, troponin I was not a reliable biomarker of myocardial damage. Instead, the authors reported a significant increase in NT-pro BNP, a biomarker that increases in heart failure and that is expressed during cardiac overload [69, 70]. Despite these results, actually the use of biomarkers, in patients treated with radiotherapy, cannot be recommended in clinical practice and remains a field of scientific research.

Prevention and Future Perspectives

It is clear that mediastinal radiotherapy increases the risk of heart disease. Prevention of RIHD is a crucial moment in the management of cancer patients undergoing radiotherapy. This is possible thanks to advances in radiotherapy and preventive intervention on the patients.

The use of better conformal radiation-computerized techniques (involved-node and involved-site radiation) helps both to decrease the doses of radiation administered (excess related risk for Gy 7.4%, 95% confidence interval 3.3–14.8%) [71] and to decrease the field and the volume of tissue to be irradiated [72]. In cases of breast cancer, for example, today it is possible to significantly limit the field of radiation exposure by avoiding internal mammary irradiation or by practicing partial breast irradiation (PBI) in patients considered to be at good prognosis [73].

Moreover, the introduction of new-generation methods such as proton beam therapy (PT) and intensity-modulated radiotherapy (IMRT) has improved the results of radiotherapy compared to conventional three-dimensional techniques [74, 75]. It is advisable, especially in thoracic neoplasms, to keep the mean dose of RT <26Gy and V30 < 46% because this significantly reduce the risk of pericarditis, although it is necessary to meet the dose-volume constraints before the treatment plan is constructed. In particular, IMRT and proton therapies reduced the mean dose of radiation to both valves and ventricles. Furthermore, it has been shown that different breathing approaches (deep inspiration breath-hold versus free breathing) are related to a lower heart dose [76, 77].

Since this type of approach is not always feasible, it is suggested to also take into account the patient's comorbidities and life expectancy to establish the right treatment plan [78].

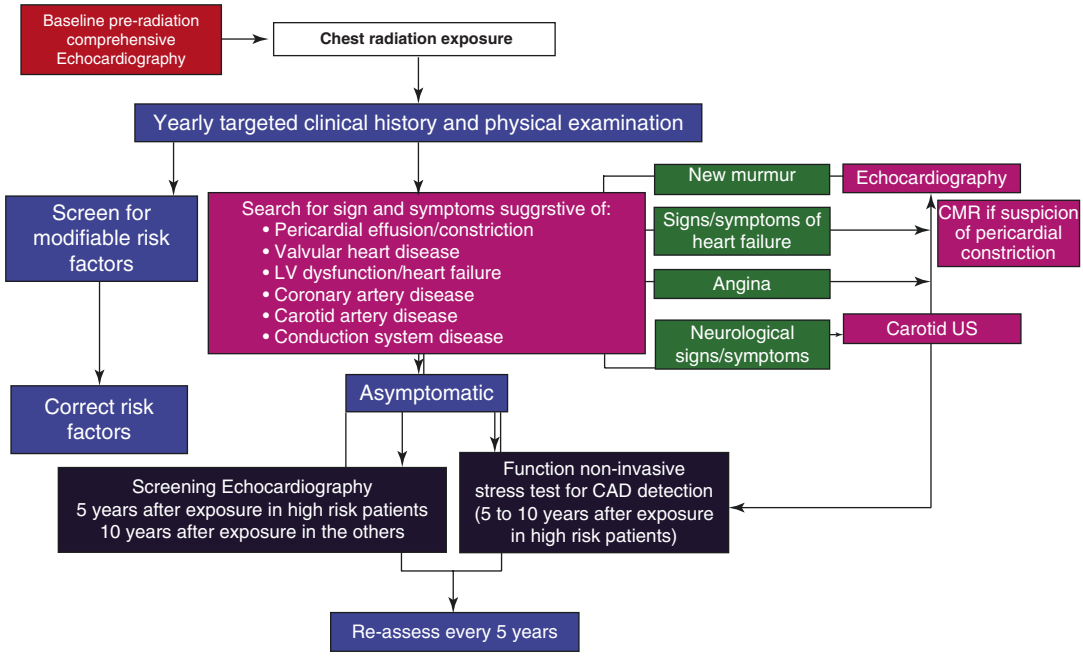

Fig. 4.3 Algorithm for patient management after chest radiotherapy. (From Lancellotti and Nkomo [80]. Reproduced with permission of Oxford University Press on behalf of the European Society of Cardiology)

Beside modulating radiotherapy, another aspect to be considered to reduce the risk of RIHD is to identify and treat cardiovascular risk factors in each patient. Particularly, it is important to correct modifiable risk factors and to optimize the treatment of concomitant cardiac disease. It is fundamental to early identify cardiac damage, possibly before symptoms occur, and to start precociously cardioprotective drugs. For this reason, before starting, during, and for long time after treatment, patients should undergo cardiovascular surveillance (Fig. 4.3).

In conclusion, the prevention of RIHD represents today a primary objective for all patients undergoing radiotherapy. However, more studies are needed on larger cohort of neoplastic patients to better define the real burden of this problem and define preventive and therapeutic strategies.

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5 Cardiovascular Damage Induced by Anti-VEGF Therapy

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Introduction

Vascular endothelial growth factor and its receptor (VEGF and VEGFR) play an important role in maintaining the regular homeostasis of vascular walls. Endothelium is not a simple cellular monolayer that separates the blood from the vascular walls, but it plays a key role in the regulation of vascular function, 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 [1]. 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, 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 [2, 3]. VEGF and VEGFR transduce signaling that promote survival and function of endothelial cells. Thus inhibition of VEGF and VEGFR can cause cardiovascular toxic effects [4]. Bevacizumab is a monoclonal antibody that inhibits VEGF; it causes predominantly arterial hypertension and thromboembolic events. Tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib, regorafenib, axitinib, ponatinib) cause vascular toxicity directly through inhibition of VEGFR or indirectly by interfering with other tyrosine kinases. Heart failure caused by inhibition of VEGF and VEGFR has been rarely documented. Arterial hypertension and thromboembolic events are more frequent cardiovascular side effects. In this chapter we will illustrate the mechanism of action of anti-VEGF/anti-VEGFR drugs, their toxic effects, and the strategy to prevent, to diagnose, and to treat these cardiovascular complications.

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VEGF and VEGFR

Vascular endothelial growth factor (VEGF) is the main member of a family of structurally and functionally related cytokines, which plays a critical role in angiogenesis and promotes cell survival and growth and proliferation of endothelial cells by binding to specific receptors (VEGFR-1, VEGFR-2, neuropilin) [5, 6]. 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. 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 activates signaling pathways that promote 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 [7].
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 the inositol 3 phosphate kinase pathway, 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, promoting cell survival, while the second enzyme leads to NO formation which, in turn, promotes vasodilation and increases permeability and cell migration [8].
C. VEGFR-3 differs from the other two receptors because it moves toward 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 [9].

Anti-VEGF and Anti-VEGFR Drugs

The inhibition of VEGF and its receptors represents the main (but not sole) mechanism by which antiangiogenic drugs can cause vascular toxicity (Table 5.1) [10].

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), heart failure (HF), myocardial ischemia, and atherothrombotic events (ATEs). The incidence of severe ATEs in patients treated with bevacizumab was reported to be around 1.8%, with an incidence of AMI equal to 0.6% [11–13]. Left ventricular dysfunction was reported in 1.7–3% of cases [14].

Sunitinib is a multi-target tyrosine kinase inhibitor (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 in 4–11% [14, 15].

Table 5.1 Antiangiogenetic drugs, their targets, and their possible cardiovascular toxic effects

Drugs	Targets	Cardiovascular toxic effects
Bevacizumab	VEGF-A	Arterial hypertension+++, thromboembolism +++, heart failure (HF)++, myocardial ischemia++
Sunitinib	VEGFR-1–3, PDGFR, c-kit, FLT3, CSF-1R, RET	Arterial hypertension+++, HF+++, myocardial ischemia++, thromboembolism ++, long QT, and arrhythmias +
Sorafenib	VEGFR, PDGFR, Raf-1, B-Raf, c-kit, and FLT3	Arterial hypertension+++, myocardial ischemia++, ATEs++, HF++
Pazopanib	PDGFR, VEGFR, and c-KIT	Arterial hypertension+++, ATEs++, myocardial ischemia++, HF +
Regorafenib	VEGFR-2–3, RET, KIT, PDGFR, and RAF	Arterial hypertension+++, myocardial ischemia +
Axitinib	VEGFR-1–3	Arterial hypertension+++, myocardial infarction+, arrhythmias+, HF+
Cabozantinib	VEGF, MET, RET, KIT, Flt-3, AXL, and Tie-2	Venous thrombosis+, arterial thrombosis+

Sorafenib is a multi-target TKI that, at clinically relevant concentrations in vitro kinase assay, inhibits at least 15 kinases, including VEGFR, PDGFR, Raf-1, B-Raf, c-Kit, and FLT3 [16]. It can cause high blood pressure, myocardial ischemia, and, rarely, heart failure [17].

Pazopanib is a small molecule, multi-target inhibitor of PDGFR, VEGFR, and c-KIT. It can cause high blood pressure and congestive heart failure [18, 19].

Axitinib is a potent second-generation inhibitor of VEGFR. It can cause high blood pressure but also myocardial infarction and arrhythmias [20].

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 [21].

Cabozantinib is a potent inhibitor of receptor tyrosine kinases, including VEGF, MET, RET, KIT, Flt-3, AXL, and Tie-2. It can cause venous and, more rarely, arterial thrombosis (myocardial infarction and stroke) [22].

Mechanisms of Cardiovascular Toxicity

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 [23]. 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. VEGF binding with the VEGFR-2 activates several intracellular signaling pathways, including the phosphatidylinositol-3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways. When VEGF interacts with its receptors VEGFR-1, VEGFR-2, and VEGFR-3, 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 determines the stimulation of eNOS (endothelial nitric oxide synthase), thus causing the production of NO. In addition, Akt inhibits caspase-9, promoting cell survival. 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 Ca2+ ions in the cell. This can lead to eNOS induction and increase of NO production [24]. 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, leading to arterial hypertension and to an increase

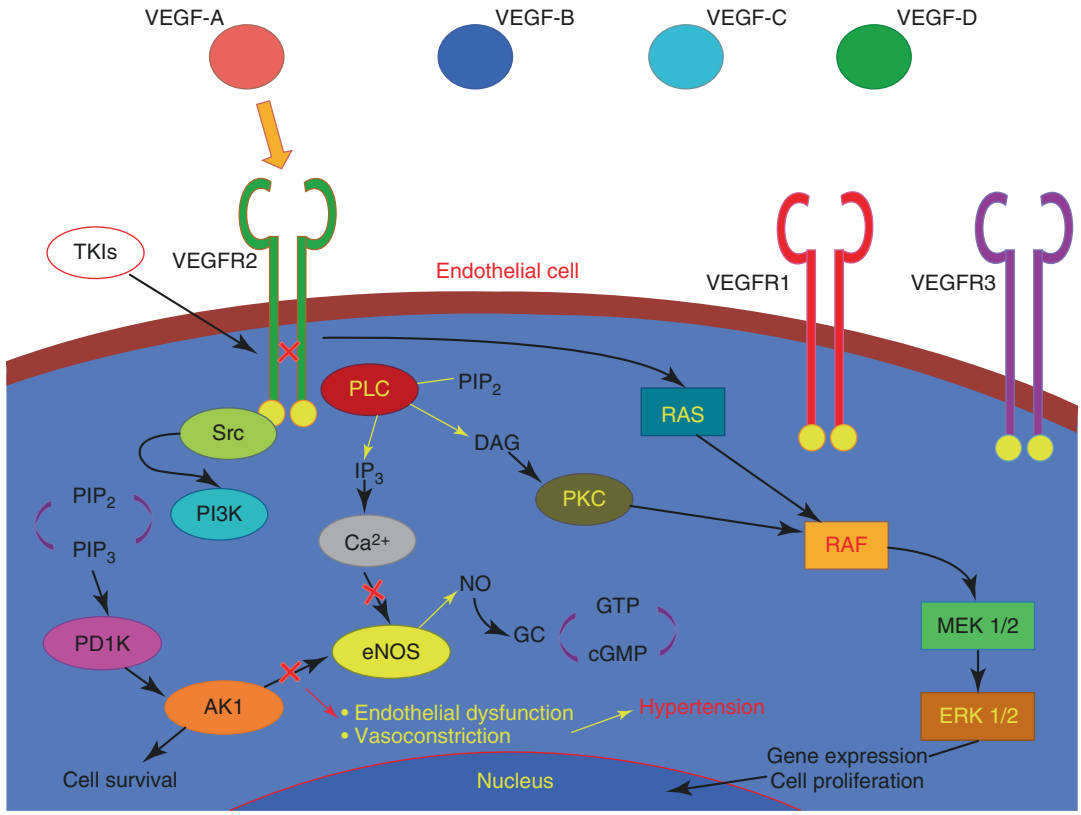

Fig. 5.1 Consequences of VEGF pathway inhibition. Reproduced from: Bronte G et al. Conquests and perspectives of cardio-oncology in the field of tumor angiogenesis-targeting tyrosine kinase inhibitor-based therapy. Expert Opin Drug Saf. 2015 Feb;14(2):253–67

of blood viscosity through the overproduction of erythropoietin [25]. Vasoconstriction is accompanied by endothelial dysfunction. Hence, increased blood viscosity related to cancer, inhibition of the VEGF/VEGFR, and endothelial dysfunction can contribute to increase the risk of arterial thrombosis (stroke and myocardial infarction) in cancer patients (Fig. 5.1) [23].

Arterial Hypertension

Several mechanisms of arterial hypertension have been postulated. These mechanisms include both functional (inactivation of eNOS and production of vasoconstrictors such as endothelin-1) and structural (capillary rarefaction) modifications [26].

VEGF inhibition decreases the production of NO leading to vasoconstriction, elevated peripheral vascular resistance, and hypertension. NO deficiency also leads to increased proliferation of vascular medial cells, creating a more resistant hypertensive state [27]. Additionally, impaired NO production affects renal sodium homeostasis, leading to sodium retention and further elevations in blood pressure [28]. Capillary rarefaction is another postulated mechanism through which VEGF inhibition can lead to hypertension. This process involves a decrease in capillary density at the peripheral level leading to increased vascular resistance. Rarefaction can be functional (vasoconstriction of arterioles) or structural (true capillary loss), although both processes are often interrelated [29]. In a study evaluating 20 patients treated with the VEGF inhibitor bevacizumab, microvascular rarefaction and hypertension were observed in all subjects [30]. This phenomenon is thought to be reversible after discontinuation of the VEGF inhib-

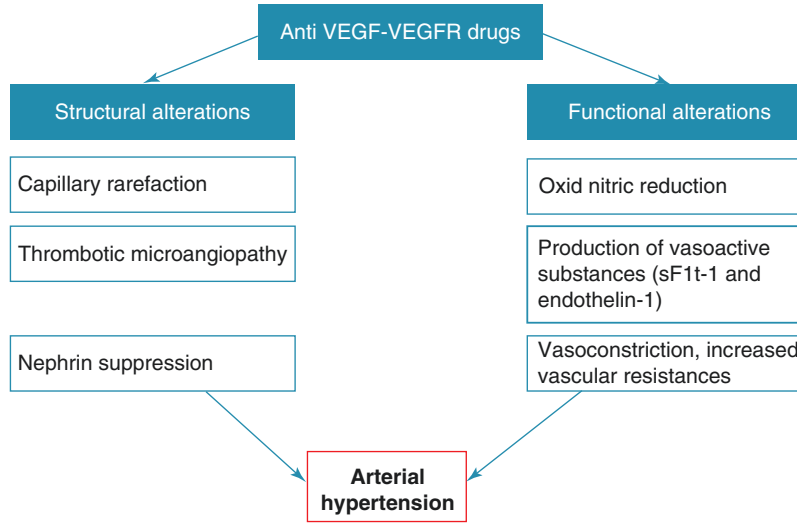

Fig. 5.2 Mechanisms leading to arterial hypertension induced by anti-VEGF treatments

itor [31]. Whether rarefaction is the cause of hypertension or a consequence of elevated pressures remains uncertain [32]. The loss of pericytes due to inhibition of PDGFR, along with inhibition of angiogenesis, due to the VEGFR inhibition, is supposed to be the main mechanisms for capillary rarefaction [33].

VEGF inhibition may also lead to increased production of other vasoactive substances which can contribute to the development of hypertension. For example, VEGF inhibition causes endothelial dysfunction and increased endogenous sFlt-1 and endothelin-1 (ET-1) production, which leads to a phenotype resembling preeclampsia with significant hypertension and proteinuria [34, 35]. Finally, hypertension due to anti-VEGF may be exacerbated by their effects on other organ systems. Renal dysfunction due to angiogenesis inhibition may also play a role in the development and maintenance of hypertension. Thrombotic microangiopathy has been observed and can lead to hypertension, proteinuria, and hemolysis. These agents can also lead to the deprivation of functional VEGF in the glomeruli resulting in deterioration of kidney function, reduced glomerular filtration rate (GFR), volume retention, and ultimately the hypertensive response [36, 37]. VEGF-mediated suppression of nephrin, which is important for the maintenance of glomerular function, can contribute to the development of arterial hypertension [38]. In addition, vascular injury can be "direct," i.e., caused directly by the target therapies such as VEGF/VEGFR, or "indirect," i.e., caused by arterial hypertension secondary to target treatment (Fig. 5.2).

Arterial hypertension was reported in patients treated with bevacizumab, axitinib, sorafenib, sunitinib, axitinib, pazopanib, and regorafenib. It is the most common cardiovascular adverse effect. In a meta-analysis including 13 clinical trials and a total of 4999 patients, the incidence of all-grade hypertension was 21.6%. The incidence of hypertension warranting the addition or adjustment to dosing of more than one medication (grade 3 or grade 4) was 6.8%. The RR of grade 3 or grade 4 hypertensions using sunitinib compared to placebo was 23 [39, 40].

Qi et al. in a meta-analysis showed that the average incidence of all-grade hypertension among patients receiving pazopanib was 35.9%. High-grade (grade 3 or grade 4) hypertension was associated with significant morbidity and subsequent dose reduction or discontinuation of pazopanib treatment. The trials reported an average incidence of high-grade hypertension among patients receiving pazopanib of 6.5% [41].

Arterial hypertension is also the most frequent cardiovascular adverse event associated with axitinib. Indeed, all-grade hypertension showed a frequency of 40%, while grade 3 or higher had a frequency of 13% [42].

Cardiac Dysfunction

Mechanisms of cardiac dysfunction induced by anti-VEGF drugs are not completely understood and some hypothesis has been formulated. For example, sunitinib may cause systolic dysfunction by inhibiting the mitogen-activated protein kinase (MAPK), a regulator of myocyte stress response. This inhibition leads to the reduction of energy production and mitochondrial and consequently ventricular dysfunction [43]. In animal models treated with sunitinib, an increase in the expression of genes involved in the response to hypoxia was observed, including the prolyl hydroxylase domain-containing protein, which is important in the regulation of the hypoxia-inducible factor 1α (HIF-1α). Hypotheses have suggested that a chronic unregulated activation of genes involved in the response to hypoxia, especially HIF-1α, may result in cardiac dysfunction. Further confirmations are required [44]. Also PDGFR inhibition induced by sorafenib and sunitinib could contribute to cardiac dysfunction. PDGFR plays an important role in promoting cell survival and cardioprotection in conditions of pathological stress [45]. Inhibition of stem cell growth factor (c-Kit or CD 117) that is expressed by hematopoietic stem cell precursors and endothelial progenitor cells may also contribute to cardiac dysfunction [46]. VEGF inhibition, in mice subjected to pressure overload, resulted in reduced capillary density, reduced compensatory hypertrophy, left ventricular dilatation, and contractile dysfunction [47]. In animal models of nonischemic cardiomyopathy, overexpression of VEGF resulted in a reduction of apoptosis and proapoptotic signals and delayed progression versus heart failure after tachy-pacing [48]. Data suggest that inhibition of VEGF may worsen myocardial function, especially in the course of pathological stresses such as increased post-loading and arterial hypertension [46]. Moreover inhibition of the ERK factor favoring cell survival through inhibition of the BRAF proto-oncogene and other molecules was hypothesized [49, 50].

Thrombotic Events

Arterial thrombotic events (ATEs) have been reported with bevacizumab through VEGF inhibition [51]. Increased blood viscosity related to cancer and the presence of cardiovascular risk factors, in association to VEGF inhibition (endothelial dysfunction, production of vasoactive substances, increased inflammation, and plaque instability), further increase the risk of arterial thrombosis in oncological patients [25].

Bevacizumab through VEGF inhibition may increase inflammation and plaque instability causing thrombus formation; it increases the release of inflammatory cytokines which activate the coagulation system [52, 53]. The incidence of thrombotic events is greater in patients treated with bevacizumab plus chemotherapy compared to patients treated with chemotherapy alone [54]. Particularly Economopoulou et al. reported ATEs in 5.5% of patients treated with bevacizumab plus chemotherapy compared to 3.1% of patients treated with chemotherapy alone. The incidence of myocardial infarction was 1.5% in patients treated with bevacizumab compared to 1% in the control group. Older age (>65 years) and a previous thrombotic episode can increase thrombotic risk [55].

In a recent meta-analysis of 12,617 patients, treatment with bevacizumab was associated with a significant increase of ATEs and particularly of myocardial ischemia but not stroke [56]. The incidence of ATEs (stroke and IMA) was 3.8% in patients with metastatic colonic carcinoma, non-small cell lung cancer, and breast cancer [57].

ATEs can also be caused by sorafenib, sunitinib, pazopanib, and axitinib. In a meta-analysis that included over 10,000 patients, the incidence of arterial thromboembolic events was analyzed. The relative risk (RR) of ATEs for TKI in comparison with controls was of 3.03. RR for sorafenib was 3.1, and it was 2.39 for sunitinib [58, 59].

In a trial by Sternberg et al., the authors showed that arterial thrombotic events occurred in 3% of pazopanib-treated patients, among these MI/ischemia 2%, cerebrovascular accident <1%,

and transient ischemic attack <1% compared with the placebo arm, in which there were none [60].

Bevacizumab should be discontinued in patients who develop severe ATE during therapy; there are no guidelines regulating restart of the drug in these patients. Treatment of ATEs during anti-VEGF and anti-VEGFR treatment is the same as that used in the absence of treatment with anticancer drugs.

Pharmacological prophylaxis for thrombotic events using cardioaspirin could be considered in oncological patients at high cardiovascular risk, before starting treatment with anti-VEGF-VEGFR if there are no contraindications. Cardioaspirin has improved survival in patients with cancer and myocardial ischemia, regardless of thrombocytopenia [61].

Venous thromboembolic events can also occur in patients treated with bevacizumab although the incidence of this event is conflicting in the different studies. From a meta-analysis, the risk of venous thromboembolic events was high in patients treated with bevacizumab; from a second one, no significant increase in the venous events was found [62].

Venous thromboembolic events are reported also in the course of treatment with TKI especially if used in combination with chemotheraphy [63]. Venous thrombotic events are currently managed using low-molecular-weight heparin; however recent evidences suggest that direct oral anticoagulant is safe and effective (see chapter on venous thromboembolism) [64].

Early Diagnosis of Cardiovascular Toxicity

In order to prevent the occurrence of cardiovascular events in patients treated with anti-VEGF-VEGFR drugs and avoid the need of treatment discontinuation, it is important that patients undergo a comprehensive cardiovascular evaluation before starting the treatment and during its course. Particularly it is mandatory to identify and manage cardiovascular risk factors and to optimize treatment of current cardiac disease [65, 66]. Cardiovascular evaluation should include objective examination including peripheral pulses evaluation, blood pressure measurement, ECG, and echocardiography. Antihypertensive treatment should be started if high blood pressure is found or therapy implemented if at control it is found to be nonoptimal. During anticancer therapy, according to the National Cancer Institute, blood pressure should be measured every week during the first cycle, subsequently every 2 to 3 weeks [67]. Antihypertensive treatment should be individualized on the basis of the risk profile of the patient; only in same cases of resistant arterial hypertension, temporary suspension of anti-VEGF-VEGFR drugs should be considered.

Echocardiography beyond measurement of ejection fraction with biplane Simpson method should possibly include 3D evaluation and left ventricle global longitudinal strain analysis to identify early signs of left ventricular dysfunction.

Carotid ultrasound should be performed in patients with risk factors to refine risk stratification. Recent studies reported the usefulness of carotid-femoral pulse wave velocity (cf-PWV) and augmentation index to early detect vascular damage in patients treated with anti-VEGFR drugs. Specifically, blood pressure (BP) and cf-PWV and systolic (global longitudinal strain) and diastolic function have been shown to change in patients after the initiation of the anti-VEGFR treatment [68]. Interestingly, changes in BP and stiffness seemed to be reversible upon discontinuation of treatment, while LV systolic and diastolic functions were persistently abnormal [69].

Treatment of Cardiovascular Toxicity

There are no specific guidelines or expert consensus regarding the optimal treatment of anti-VEGF-induced arterial hypertension and other cardiovascular complications in oncological

patients. Treatment of cardiovascular complication induced by anti-VEGF-VEGFR follows the current recommendations about heart failure, myocardial infarction, and arterial hypertension [70, 71]. Standard recommendations on arterial hypertension can also be applied in this patient population (restriction of sodium intake, exercise, diet, lifestyle changes). ACEI/sartans, calcium dihydropyridine antagonists and beta-blockers are the preferred drugs in this setting [65]. Some studies showed that ACEIs and sartans have antitumor properties; they can reduce angiogenesis and microvascular rarefaction, although recent studies have suggested that these drugs can develop a pro-tumor microenvironment [72, 73].

Diltiazem and verapamil that inhibit the cytochrome P450 should be avoided for their possible interference with anti-VEGF inhibitors, and diuretics are not drugs of choice for possible induction of electrolyte disturbances that may favor QT interval prolongation.

Considering mechanism of action of VEGF-VEGFR, drugs that increase the release of nitric oxide should be considered in resistant arterial hypertension [74]. In fact, some cases reported the efficacy of long-release nitrates in patients with antiangiogenic drugs induced hypertension despite optimized medical therapy [75].

Also sildenafil (phosphodiesterase inhibitor) and nebivolol can potentiate the vasodilatory properties of NO, and they can be effective in such patients [76]. Nebivolol, B1 adrenergic antagonist, may enhance the nitric oxide signal; it may induce vasodilatation increasing the bioavailability of NO. The exact mechanism is not known, but it may be secondary to nitric oxide synthase activation through the stimulation of β3-adrenergic receptors expressed in embryonic cells and the reduction of dimethyl arginine and free oxygen radicals [77]. Also antagonists of endothelin receptors may play a role in resistant hypertension even if their use has been validated in the treatment of pulmonary hypertension (Fig. 5.3).

In cases of resistant arterial hypertension, despite optimal medical therapy, dose reduction or temporary suspension of anti-VEGF treatment should be considered [78].

In patients at high cardiovascular risk, treatment with aspirin could be warranted before starting anti-VEGF treatment [61]. In case of documented myocardial ischemia during angio-

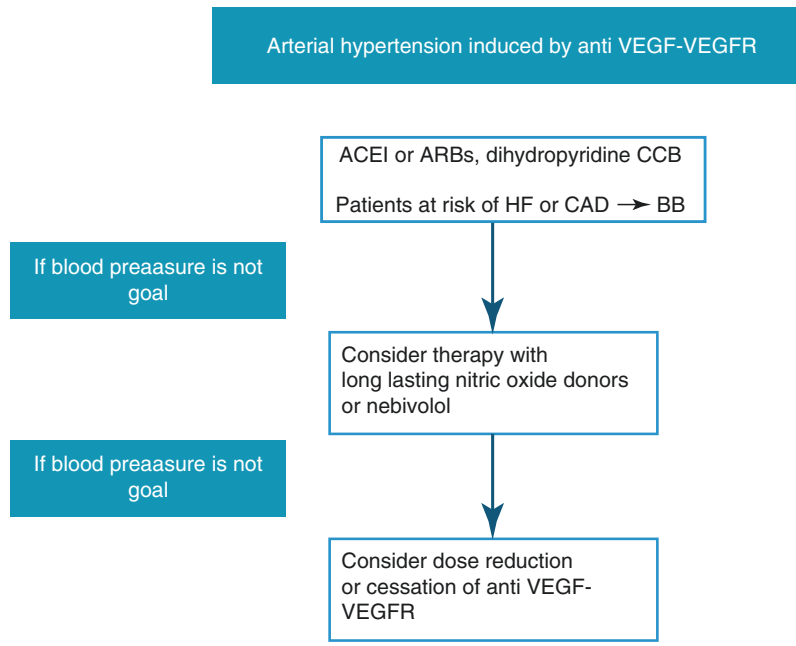

Fig. 5.3 Treatment of arterial hypertension induced by anti-VEGF treatments

genic inhibitor therapy, treatment should be suspended and eventually therapy resumed, after healing if benefits outweigh the risks. In case of myocardial infarction, the permanent discontinuation of the drug should be considered.

If asymptomatic LV dysfunction occurs, angiogenic inhibitors should be continued in cases of mild (ejection fraction reduction >15%, with ejection fraction >50%) or moderate decrease (ejection fraction 50–40%). Only in case of severe LV dysfunction (ejection fraction <40%) and in symptomatic patients, it is recommended to stop anticancer therapy [74].

LV dysfunction should be treated according to current recommendation. Resumption of the drug can be considered upon ejection fraction improvement and the normalization of symptoms, but the evidences on this regard are still unclear [79].

Conclusions

Anti-VEGF-VEGFR drugs cause cardiac and vascular toxicity, especially arterial hypertension and arterial thrombotic events. Given the high incidence of arterial hypertension induced by VEGF/VEGFR inhibitors, it is very important to control blood pressure 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. Moreover, optimization of treatment of concomitant cardiovascular disease is advisable. Echocardiographic monitoring of cardiac function is also reasonable. There are no standardized guidelines regarding the timing of monitoring patients undergoing this treatment; however baseline evaluation and routine periodical surveillance during treatment (i.e., every 3 to 6 months in the absence of symptoms) is reasonable.

More and wider prospective studies are needed to clarify pathophysiological mechanism of cardiovascular damage induced by anti-VEGF inhibitors and to better delineate how to manage patients.

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6 Cardiovascular Damage Induced by Anti-BCR-ABL TKIs

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Introduction

In recent years important advances have been made in the field of oncology leading to improved survival of cancer patients, but the impact of cardiovascular complications in terms of morbidity and mortality is also increasing.

Target therapy was recently introduced to allow a more selective antineoplastic effect thus reducing the impact of side effects, including the cardiovascular ones. However, also these drugs are burdened by a certain cardiovascular toxicity, even if lower. In this chapter, we will illustrate the mechanisms of action of anti-BCR-ABL TKIs, their adverse effects and the mechanisms responsible of cardiovascular toxicity.

Anti-BCR-ABL TKIs are drugs especially used in the treatment of hematological cancer and gastrointestinal stromal tumors (GISTs). They inhibit the BCR-ABL tyrosine kinase, encoded by the chimeric gene BCR-ABL, obtained by the reciprocal translocation between chromosomes 9 and 22. This gene plays a central role in the pathogenesis of Philadelphia (Ph) chromosome-positive leukemia, notably chronic myeloid leukaemia (CML) [1]. Three fusion proteins can be formed as a result of breakpoint in BCR, all of which exhibit deregulated protein tyrosine kinase activity. Basic mechanisms that have been attributed to BCR-ABL-positive cells, particularly in CML, are increased proliferation, increased resistance to apoptosis, and an alteration of their adhesion properties [2].

Anti-BCR-ABL TKIs includes old- and new-generation drugs. First-generation drug is imatinib. Second-generation drugs are dasatinib, nilotinib, and bosutinib; third-generation drug is ponatinib [3]. Especially second- and third-generation drugs can cause cardiovascular complications such as arterial thrombosis, myocardial ischemia, QTc prolongation, and, less frequently than conventional chemotherapy, myocardial dysfunction.

A considerable number of patients may acquire resistance to imatinib because of the development of a point mutation in the BCR-ABL1 fusion gene. Second-generation TKIs—dasatinib, nilotinib, and bosutinib—have been shown to be effective in imatinib-resistant patients, and more rapid in achieving a deep molecular response. Ponatinib, a third-generation

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TKI specifically designed to overcome resistance caused by a T315I mutation in BCR-ABL1 kinase, has exhibited high clinical efficacy in patients with multi-TKI-resistant CML [4, 5].

Thus the inhibition of BCR-ABL kinase by small molecules has profoundly improved the prognosis of patients with several forms of chronic leukemia and some forms of gastrointestinal stromal tumors [6]. However, these drugs can cause cardiovascular complications. Initial reports suggested a risk for imatinib-induced cardiotoxicity, but analysis of large cohorts did not confirm these data [7].

Severe atherosclerotic and non-atherosclerotic peripheral artery disease (PAD) can occur (in up to 30%) in patients treated with nilotinib and ponatinib, even in the absence of cardiovascular risk factors, although the latter increases the likelihood [8]. PAD can occur as early as in the first months of therapy or as a late effect several years after treatment [9].

Other complications potentially associated with anti-BCR-ABL TKIs are myocardial infarction and stroke. In addition, QT prolongation, pleural effusions, and both systemic and pulmonary hypertension have also been observed [10]. It is essential for both cardiologists and oncologists to possess knowledge of these issues in order to develop appropriate monitoring and risk mitigation strategies to prevent these toxicities and avoid premature cessation of the drug. Incidence and mechanisms of these adverse events will be better described subsequently. Tables 6.1 shows mechanism of action of anti-BCR-ABL TKIs.

Table 6.1 Anti-BCR-ABL TKIs, mechanism of action

Drugs	Mechanism of action
Imatinib	ABL, c-KIT, PDGFRs (α and β) inhibition
Dasatinib	BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ inhibition
Nilotinib	BCR-ABL, PDGF, cKIT, PDGFR, CSF-1R, DDR1 inhibition
Ponatinib	BCR-ABL1t315I, VEGFR2, FGFR1; TIE2, Flt3, Src, PDGFRα, RTK inhibition
Bosutinib	BCR-ABL1t315I, Src inhibition

Anti-BCR-ABL TKI (Mechanism of Action and Cardiovascular Adverse Effects)

Imatinib inhibits ABL, c-KIT, and platelet-derived growth factor receptor (PDGFRs α and β). It has been approved by the FDA as an oral drug for the treatment of CML, gastrointestinal stromal tumors (GISTs), and hypereosinophilic syndrome [11]. Despite initial reports suggested a discrete risk for imatinib-induced cardiotoxicity, analysis of large cohorts showed that it is an uncommon event [7], reporting an incidence ranging from 0.5% to 1.7% [7, 12].

Several mechanisms were hypothesized to explain cardiac dysfunction in patients treated with imatinib. In some reports it has been implicated the inhibition of cAbl; however, in other experimental studies, mice with cAbl mutation didn't develop cardiotoxicity [13]. The inhibition of GATA 4, a factor that promotes cell survival and adaptative response to stress in adults, was also hypothesized to be responsible of cardiac dysfunction. Mice without GATA 4 were more likely to develop cardiotoxicity [14]. Furthermore, imatinib cardiotoxicity could be related to mitochondrial dysfunction, with secondary apoptosis promoted by oxidative stress, increased by age [15].

According to other studies, imatinib is not cardiotoxic in clinical doses, its cardiotoxicity increases with high doses; it is favored in old patients with comorbidity such as heart failure and renal failure [16]. Moreover imatinib seems to be effective in the reduction of glycemic values and in the treatment of pulmonary hypertension, through inhibition of PDGFR that is overexpressed in pulmonary artery cells and the inhibition of c-KIT [17–19]. In experimental models, imatinib seems to have also anti-atherosclerotic activity [20]. Other studies found that imatinib can attenuate myocardial remodeling and improve left ventricular diastolic dysfunction in spontaneously hypertensive rats by affecting the PDGFR pathway without the blood pressure-lowering effect [21].

The incidence of edema and dyspnea was reported to be as high as 66% and 16%, respectively [22]. This is probably due to imatinib's inhibition of PDGFR [23]. Paradoxically, imatinib treatment can also protect against brain and lung edema during stroke and lung injury, respectively [24].

Table 6.2 reports the main cardiovascular adverse events mediated by anti-BCR-ABL TKIs and the possible positive effects.

Dasatinib inhibits BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. It is used as second-line treatment for chronic myeloid leukemia. It can induce pleural effusion, fluid retention, and severe precapillary pulmonary hypertension [25].

Table 6.2 Anti-BCR-ABL TKI cardiovascular adverse events and positive effects

Drugs	Cardiovascular adverse events	Positive effects
Imatinib	Rare (Myocardial dysfunction in few cases)	Reduction of pulmonary hypertension Reduction of glycemic values Safe cardiovascular risk profile
Dasatinib	Pulmonary hypertension Pleural effusion QT interval prolongation	
Nilotinib	Peripheral arterial disease (PAD) Cerebrovascular events Coronary artery disease QT interval prolongation Hyperglycemia, Hyperlipidemia	
Ponatinib	Peripheral arterial disease (PAD) Myocardial infarction Cerebrovascular events Arterial hypertension QT interval prolongation Venous thromboembolism	
Bosutinib	Rare	

For several years, the cardiovascular safety profile of dasatinib was wrongly considered similar to that of imatinib, with the exception of pleural effusion, which has been observed since the first use of the drug [26].

Subsequently, pulmonary hypertension (PAH) as complication of dasatinib therapy was detected. A transient significant increase of pulmonary arterial pressure detected by echocardiography was observed for the first time in 2007 among patients with pleural effusion [27]. Subsequently, other reports of PAH not associated with pleural effusion emerged [28, 29]. A recent assessment of all causes of dasatinib-related PAH confirmed by catheterization (41 patients) showed that compared with other etiologies, dasatinib-induced PAH is associated with partial to complete reversibility after drug discontinuation [30, 31]. This data was not confirmed by the French PH registry in which most of the patients did not experience complete recovery after dasatinib withdrawal, and two died [28]. Analysis of the FDA database designed to support postmarketing surveillance found that PAH was associated with dasatinib and not with other TKIs and that it often occurred in patients with cardiovascular risk factors or a medical history of cardiopulmonary events [32].

In the French registry, incidence of pulmonary hypertension caused by dasatinib was found in 0.45% of patients [28]. This condition usually appears 8–40 months after exposure to dasatinib, with suggestive clinical and hemodynamic presentation. The exact mechanism by which dasatinib causes pulmonary hypertension is not known. Preclinical studies suggested that an imbalance in the expression of PDGFR contributes to the excessive proliferation of smooth muscle cells in newly born sheep with pulmonary hypertension [33]. But considering that dasatinib and imatinib both inhibit the PDGFR and imatinib is effective in treating pulmonary hypertension through the blockade of PDGFR, another mechanism independent of PDGFR should be responsible [34].

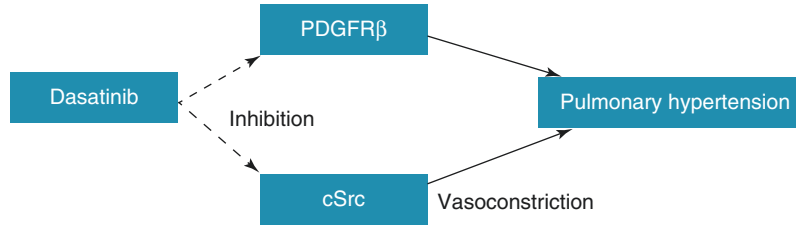

Fig. 6.1 Mechanisms possibly implicated in the development of pulmonary hypertension induced by dasatinib

Considering that the main differences between imatinib and dasatinib are related to the inhibition of Src-type kinases, Src kinases may be responsible for PAH by dasatinib [35]. Preclinical studies suggest that Src kinases induce vasoconstriction and hypoxia in the pulmonary arteries of rats. cSrc is in fact abundantly expressed in vascular cells, and its activation intervenes in smooth muscle cell proliferation and vascular tone regulation through various signal transduction pathways. Inhibition of cSrc causes Ca2+ channel activation by K+− and voltage-dependent channel activation (Kv 1.5) and vasoconstriction (Fig. 6.1) [23].

Pleural effusion was found in 7–35% of patients treated with dasatinib, less in patients treated with imatinib, and <1% in patients treated with nilotinib. Fluid retention grade 3–4 was found in 8% of patients, including pleural and pericardial effusion, respectively, in 7% and 1% of patients [36]. Inhibition of PDGFRβ and other kinases is also responsible of fluid retention [37, 38]. Pleural effusion requiring drug discontinuation occurs in <10% cases [29]. The cause of pleural effusion can also be immunity-mediated, considering the high frequency of lymphocytes in pleural fluid and tissue and the association with skin rash or history of autoimmunity [39]. In addiction, it has been suggested that an immune-mediated mechanism underlying the occurrence of pleural effusion could help to promote tumor regression. Patients who develop lymphocytosis and increased levels of specific lymphocyte subsets in association with pleural effusion have a major molecular response rate and better progression-free and overall survival than patients who do not [40, 41].

Recent clinical trials have evaluated the incidence of coronary, cerebral and peripheral thrombotic events in dasatinib-treated patients. A recent meta-analysis showed that the use of dasatinib is associated with a significant increase in the risk of CV events. In a population-based cohort study, the incidence of myocardial infarction was 2.4 times higher in patients treated with dasatinib than in those treated with imatinib [42].

Nilotinib inhibits BCR-ABL, PDGF, cKIT, PDGFR, CSF-1R, and DDR1. It is a second-generation drug used as a second line in the treatment of chronic myeloid leukemia. It can cause myocardial ischemia, QT prolongation, and arterial thrombosis. Nilotinib and ponatinib, the latter third-generation TKI, are associated with a high risk of vascular events. According to a recent meta-analysis involving 29 studies and 15,706 patients with chronic myeloid leukemia, the incidence of major arterial vascular events was 0.8% in patients not treated with TKI, 1.1% in patients treated with dasatinib, 0.1% in patients treated with imatinib, 0.4% for bosutinib, 2.8% for nilotinib, and 10.6% for ponatinib. The relative risk (RR) for nilotinib compared with imatinib suggested a significantly increased risk of the composite of major arterial events with nilotinib treatment (RR 5.3; 95% CI 3.0–9.3, $p < 0.001$). This study demonstrated that patients who received nilotinib or ponatinib had a greater number of major arterial events when compared to non-TKI-, imatinib-, dasatinib-, and bosutinib-treated patients [43].

Major arterial events induced by nilotonib include obstructive peripheral arterial disease (PAD), myocardial infarction, and cerebrovascular diseases [44, 45]. Cardiovascular risk factors can increase the risk of vascular events although there were cases of patients treated with nilotinib with vascular events and without

cardiovascular risk factors. Certainly, patient's comorbidities increase the risk of developing arterial vascular events [46]. A retrospective cohort study of CML patients treated with nilotinib found that patients with a pre-existing high/very high risk for cardiovascular disease were significantly more likely to develop an arterial occlusive event [47]. In addiction, nilotinib seems to cause accelerated atherosclerosis [48]. The pathophysiology of TKI-related arterial events remains unclear, and it is thought to be multifactorial [49]. Different mechanisms were hypothesized [50–52]. Diabetes mellitus cases after nilotinib have been documented, and in some cases of PAD there was a predominant involvement of peripheral and small vessels as in diabetes. Thus probably nilotinib-induced diabetes mellitus could contribute to the development of peripheral arteriopathy. Moreover, lipid profile disturbance (high total cholesterol, high LDL cholesterol, or low HDL cholesterol) was also detected among 18–57% of patients receiving nilotinib [53, 54]. These metabolic perturbations may increase a patient's risk of cardiovascular events. Another proposed mechanism of TKI-induced arterial vascular diseases is a change in vessel wall homeostasis. Nilotinib in vitro was demonstrated to inhibit proliferation of endothelial cells and angiogenesis [55]. Abnormalities of the vascular endothelium related to the use of TKIs are potentially the result of TKI binding to non-BCR/ABL fusion proteins which include discoid domain receptor 1 (DDR1), platelet-derived growth factor receptor (PDGFR), or KIT [56]. DDR1 was recently implicated in the formation of atherosclerotic plaque [57]. Mice without this receptor had an increase in plaque formation. In other studies, this datum was not confirmed [58].

The inhibition of KIT and PDGFR, which regulate vascular and perivascular cells, also contributes to the development of vascular adverse events. KIT regulates survival, growth, and hypertrophy of mast cells that contain important repair molecules such as histamine, epinephrine, and tissue activator of plasminogen, whose production and release are dependent on KIT [59]. Therefore, a deactivation of mast cells contributes to a reduced vascular repair and predisposes to thromboembolic and atherothrombotic events. On the other hand, KIT is also inhibited by the imatinib and it does not cause PAD; therefore, certainly other factors and other kinases which are not yet known intervene in nilotinib-related PAD [44].

It remain uclear if pretreatment with imatinb has a role in the development of arterial disease induced by nilotinib or a protective one because it reduces blood glucose levels. Besides pre-existing cardiovascular risk factors, also genetic factors may contribute to the development of PAD in patients treated with this drug [13]. Moreover nilotinib can increase pancreatic enzymes (lipase and amylase), hyperbilirubinemia and hyperglycemia [60, 61].

QT prolongation is another adverse effect of nilotinib and serial ECGs are recommended to follow up patients treated with this drug. Moreover it is important to prevent and eventually correct electrolyte abnormalities and to avoid concomitant drugs potentially responsible for QT interval prolongation [62, 63]. However, subsequent trials found no alarming signals of QT-related ventricular arrhythmias in patients treated with nilotinb [64, 65]. Clinical studies did not report ventricular dysfunction induced by nilotinib. This finding concurs with experimental data showing that nilotinib and imatinib produce little or no damage to cardiomyocytes, in comparison with dasatinib, bosutinib, and ponatinib [66]. Figure 6.2 shows mechanisms possibly implicated in nilotinib-mediated vascular toxicity.

Ponatinib inhibits unmutated and all mutated forms of BCR-ABL, including T315I, the highly drug therapy-resistant missense mutation of BCR-ABL. It also inhibits other tyrosine kinases including those associated with vascular endothelial growth factor receptors (VEGFR2) and fibroblast growth factor receptors (FGFR1), tyrosine kinase receptor TIE2 and FMS-related

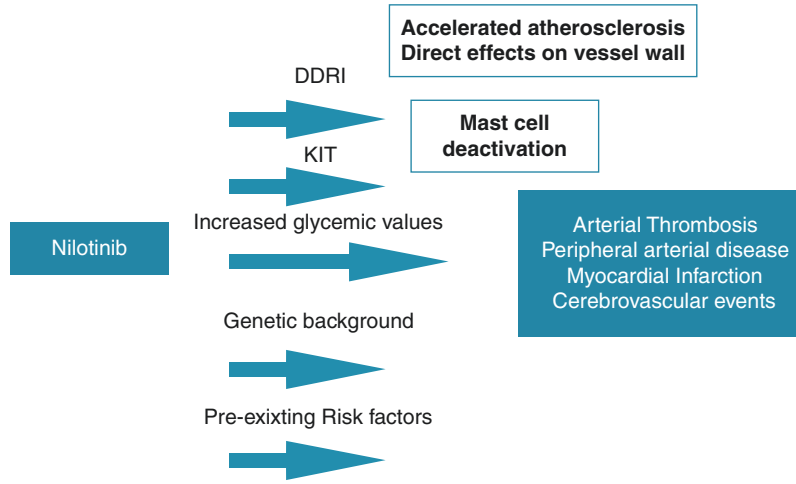

Fig. 6.2 Mechanism possible implicated in nilotinib-mediated vascular toxicity

tyrosine kinase receptor-3 (Flt3), Src, PDGFRα, and RTK (these inhibitions result in the inhibition of cellular proliferation and angiogenesis and may induce cell death) [67].

In a Phase II trial, ponatinib was associated with an incidence of 17.1% of arterial thrombotic events [5, 68]. A pharmacovigilance statement has attributed to the ponatinib an increased risk of arterial disease and thrombosis [69]. For this reason, ponatinib was stopped for a period in the market, and it was reintroduced by the FDA in January 2014, after a reassessment of the benefit/risk ratio of ponatinib with a recommendation to take appropriate measures to mitigate adverse effects in patients [70]. The mechanisms of ponatinib cardiovascular toxicity are still poorly understood. It is unknown if ponatinib alone is able to induce atherothrombotic events, if pretreatment with nilotinib is the favoring agent, or if there is a synergistic action between nilotinib and ponatinib considering that the majority of such events occurred in patients pre-treated with nilotinib [71]. The presence of cardiovascular risk factors facilitate the occurrence of ponatinb induced cardiovascular toxicity.

Correction of cardiovascular risk factors, blood glucose control and glycated hemoglobin is crucial before starting the treatment. However, atherothrombotic events with nilotinib were also observed in patients without cardiovascular risk factors. In addition, an ankle-arm index and a carotid echo-Doppler should be obtained to better stratify cardiovascular risk. In the case of PAD occurring during ponatinib therapy, it is mandatory to suspend the drug and evaluate other treatment options. Ponatinib can cause arterial hypertension through inhibition of BCR-ABL1t315I mutation and VEGFR2 [72].

Probably, inhibition of VEGFR2 is the main responsible of arterial hypertension (through reduction of nitric oxide production, capillary rarefaction, production of vasoactive substances such as endothelin I) [49, 73].

Probably ponatinib could cause cardiac damage through mitochondrial dysfunction and apoptosis [74]. There were few reported cases of pulmonary arterial hypertension in patients treated with ponatinib.

Considering the high incidence of vascular events with ponatinib, diagnostic and pharmacological measures should be used to reduce the CV risk and to improve the therapeutic safety of ponatinib in the clinical setting.

Bosutinib is a second-generation, dual Src/Abl TKI lacking significant PDGFR or c-KIT binding properties. Bosutinib is currently approved only for patients with Ph1 chronic-phase CML who were resistant to or intolerant of previous TKI therapy. It had the ability of inhibiting mutation of T3151. Studies that

evaluated bosutinib documented a low incidence of cardiac and vascular events [75]. Similar to other TKIs, the incidence of adverse events was higher in second- or later-line treatment compared with first-line treatment. Heart failure and coronary or PAD-related events were rare, suggesting that the cardiotoxic profile of bosutinib differs from that of other second- or third-generation TKIs. Most events occurred within the first year of therapy, and very few patients discontinued treatment because of these events, which were mostly managed with concomitant medications [76]. Thus vascular and cardiac event incidences in leukemia patients receiving bosutinib are generally low, even after long-term treatment, and not significantly different from those observed in imatinib-treated patients. Pericardial disorders occurred more often in bosutinib-treated patients than in those treated with imatinib [77]. Likewise, dose adjustments and discontinuations due to these events were rare; therefore, bosutinib could be considered among the treatment options for patients with cardiac or vascular comorbidities.

Management of Patients Treated with Anti-BCR-ABL TKIs

Given the toxic cardiovascular effects of anti-BCR-ABL TKIs, especially nilotinib and ponatinib, optimization of the cardiovascular risk profile should be considered before starting this treatment.

In all patients, during a baseline visit, stratification of cardiovascular risk should be performed, in agreement with ESC guidelines on cardiovascular prevention [78]. Physical examination (including blood pressure, heart rate, peripheral pulses), exhaustive blood test panel (blood count, glucose, urea, creatinine, LDL and HDL cholesterol, triglycerides, fibrinogen, VES, sodium, potassium, calcium, magnesium, TSH, uric acid, homocysteine, HbA^{1c}), electrocardiography with QT and QTc evaluation, and echocardiography should be performed in all patients. Echocardiography data should consider not only left ventricular function with ejection fraction but also diastolic function, presence of valvular disease, arterial pulmonary pressure, and possibly myocardial deformation indices to identify early signs of cardiac dysfunction. In patients with previous myocardial infarction, without a recent stress test, a provocative cardiac stress test could be performed before the beginning of nilotinib therapy, according to general clinic conditions and cardiologist suggestion [79].

As for PAD risk, a vascular evaluation is recommended: the Edinburgh Claudication Questionnaire has a good sensitivity for identification of symptomatic PAD patients [80]. In asymptomatic patients with risk factors or absence of a peripheral pulse, ankle-brachial index (ABI) should be measured. Measurement of carotid intima-media thickness and/or screening for atherosclerotic disease by carotid artery ultrasound should be considered in asymptomatic adults at moderate risk. Arterial stiffness using either aortic pulse wave velocity (PWV) or arterial augmentation index could be used to improve risk classification [81].

The decision to initiate an antiplatelet agent as anti-thrombotic prophylaxis in onco-hematological patients does not have a confirmation in literature or guidelines; however, it can be administered according to clinical opinion, based on the personal evaluation of the clinician about disease or therapy-related thrombotic risk and patient's features [82].

When antiplatelet drugs are prescribed, platelet count should be checked periodically, and prophylaxis should be discontinued when platelet count decreases to below 50,000 μL. Moreover, patients should be carefully monitored for an increased risk of bleeding due to possible interferences of ponatinib with platelet function [83].

The optimal management of patients at risk of PAD remains controversial. Certainly, prevention and correction of cardiovascular risk factors remain the most powerful tool to prevent severe cardiovascular complication during oncological treatment.

Conclusions

Second- and third-generation anti-BCR-ABL TKIs (especially nilotinib and ponatinib) cause vascular toxicity, such as arterial thrombosis (myocardial infarction, peripheral arterial occlusive disease, cerebrovascular events) with several mechanisms [84, 85]. Cardiovascular risk factors seem to increase the risk to develop vascular events. Therefore, it is very important that before starting treatment with these drugs, patients undergo a careful cardiovascular examination with the aim of stratifying the cardiovascular risk, aggressively correct cardiovascular risk factors (diabetes, hypertension, smoking, and dyslipidemia). Moreover it is advisable to investigate the presence of preclinical signs of atherosclerosis through objective examination, ABI measurement, or carotid arteries ultrasound scan and to optimize the treatment of concomitant cardiac disease. The risk/benefit ratio before starting these TKIs should be balanced by the oncological team and less cardiotoxic drugs should be preferred, in patients at a high risk of cardiovascular disease or with previous cardiovascular events. In patients undergoing treatment with dasatinib a redoubtable event is the development of PAH, and therefore echocardiographic follow-up is advisable. Imatinib and bosutinib seem to be the drugs with the most safe cardiovascular profile. More studies are needed to better investigate the burden of vascular toxicity of these drugs, to understand the exact mechanisms of cardiotoxicity, and to delineate the optimal management.

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7 Heart Failure and Left Ventricular Dysfunction

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Definition and Epidemiology

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. The current definition of HF restricts itself to stages at which clinical symptoms are apparent. Before clinical symptoms become overt, patients can present with asymptomatic structural or functional cardiac abnormalities (systolic or diastolic left ventricular [LV] dysfunction), which are precursors of HF [1].

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HF and LV dysfunction are the most concerning and serious cardiovascular complications of cancer therapies and cause an increase in morbidity and mortality. Cardiovascular (CV) complications of cancer therapy, particularly congestive heart failure (CHF) and cardiomyopathy, have been recognized since the 1970s [2].

Although cancer and CV disease remain the two most common causes of mortality in the United States, survival for both conditions has improved dramatically (Fig. 7.1). The death rate for all cancers declined by 22% between 1991 and 2011, driven by both improved diagnostic and therapeutic modalities [3]. Despite these advances, there is increasing recognition that many cancer patients experience CV complications as a result of their therapies. This includes the development of newly diagnosed CV problems or the exacerbation of previously identified CV disease.

Rates of cardiotoxicity (CTX) from cancer-related therapeutics have been reported to be in excess of 30%, with some events occurring several decades after the completion of treatment [4–6]. In addition, cardiac toxicity is the second most common cause of morbidity and mortality in cancer survivors [7]. Rates of CV disease have been reported between 3% and 24% among childhood cancer survivors who have reached the fourth decade of life (ages 30–39) [8, 9]. Complications of many cancer therapeutics, including anthracyclines and radiation, may not become apparent for more than 10 years post-treatment, and therefore

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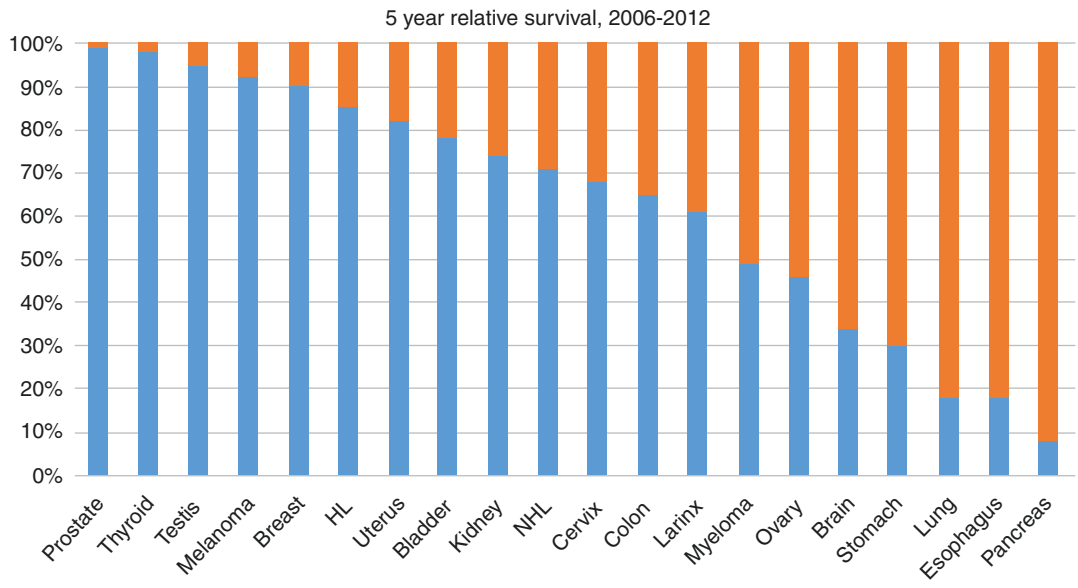

Fig. 7.1 A 5-year relative survival (2006–2012) by cancer type. (Data sources: Surveillance, Epidemiology, and End Results (SEER) 18 registries, National Cancer Institute. 2016)

these patients require long-term cardiovascular monitoring by cardio-oncologists.

Cancer Therapies and Left Ventricular Dysfunction

Antineoplastic treatments can induce left ventricular dysfunction that appears early after exposure and, therefore, may adversely affect oncological therapy or late toxicity generating cardiac injuries resulting in clinical problems only years later [10]. Table 7.1 provides an overview of the incidence of LV dysfunction with different chemotherapeutic drugs.

Anthracyclines and Other Conventional Chemotherapies

Anthracyclines are highly effective treatment of solid tumours and haematological malignancies; however, their use may cause irreversible cardiac damage characterized by continuous progressive decline in left ventricle ejection fraction (LVEF). The most accredited interpretation of anthracyclines CTX implies the increase, through the formation of iron complexes, of reactive oxygen species, which results in mitochondrial dysfunction, changes in calcium homeostasis and contractile function, and loss of cardiomyocytes by apoptosis (Fig. 7.2) [11–14].

However, there is considerable variability among patients in their susceptibility to develop anthracycline-mediated damage. Factors associated with risk of cardiotoxicity during treatment with anthracyclines are cumulative dose, female sex, elderly and paediatric population (>65 and <18 years), renal failure, concomitant or previous radiation therapy involving the heart, concomitant chemotherapy (alkylating or antimicrotubule agents, immunotherapy and targeted therapies), and pre-existing conditions such as cardiac diseases, arterial hypertension, and genetic factors [10].

Depending on when cardiac abnormalities appear, the cardiotoxicity of anthracyclines may be acute or chronic with early or late occurrence. Acute toxicity, represented mainly by supraventricular arrhythmia, transient LV dysfunction, and electrocardiographic (ECG) changes, develops in 1% of patients immediately after infusion and is usually reversible. However, acute cardiac dysfunction may also reflect myocyte injury that eventually can evolve into early or late cardiotoxicity [10].

Chronic early toxicity occurs within the first year of treatment, while late effects manifest

Table 7.1 Incidence of left ventricular dysfunction associated with chemotherapy drugs

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin)	
400 mg/m^2	3–5
550 mg/m^2	7–26
700 mg/m^2	18–48
Idarubicin (>90 mg/m^2)	5–18
Epirubicin (>900 mg/m^2)	0.9–11.4
Mitoxantrone >120 mg/m^2	2.6
Liposomal anthracyclines (>900 mg/m^2)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide	
<10 g/m^2	0.5
12.5–16 g/m^2	17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20
Bevacizumab	1.6–4
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellaneous	
Everolimus	<1
Temsirolimus	<1

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themselves after several years (median of 7 years after treatment) [15, 16]. In patients treated with commonly used anthracycline doses and >65 years of age, the rate of anthracycline-associated HF can be as high as 10% [17].

Although anthracycline-induced cardiomyopathy may develop even after decades after anthracyclines therapy, usually, CHF is clinically established at a median time of 3 months after the last dose of the drug. Tachycardia and fatigue are followed by shortness of breath, pulmonary oedema, and malignant arrhythmias. Autopsy reveals fibrosis and residual myocyte hypertrophy.

Because of their cardiotoxicity (CTX), anthracyclines are currently used less frequently than in the past. Nevertheless, they are still the backbone of the treatment of many solid and haematological tumours, including breast and gastric cancer, sarcoma, leukaemia, and lymphoma [18].

Other conventional chemotherapies that can induce myocardial dysfunction and HF are cyclophosphamide, cisplatin, ifosfamide, and taxanes (paclitaxel and docetaxel).

Alkylating agents, in particular cyclophosphamide, at high dose rarely determine left ventricular dysfunction after 10 days from the last dose of the drug with tachycardia, pulmonary oedema, and ventricular dilatation. Other alkylating agents similar to cyclophosphamide, such as cisplatin and ifosfamide, infrequently cause HF due to several pathological effects, including myocardial ischaemia.

Docetaxel, a drug frequently used in breast cancer, in combination with or after anthracyclines, cyclophosphamide, or trastuzumab, also appears to increase the incidence of HF [10, 19].

Immunotherapies and Targeted Therapies

In recent years, immunotherapies and targeted therapies have led to substantial improvement in the prognosis of cancer patients.

Target therapy blocks the growth of cancer cells by interfering with specific targeted molecules needed for cell proliferation and tumour growth [20]. Target therapy may affect by "on-target" or "off-target" toxicities. On-target refers to excessive and adverse pharmacologic effects at the target of interest, shared by all agents that reliably inhibit a specific target. Off-target refers to adverse effects as a result of modulation of other targets [21].

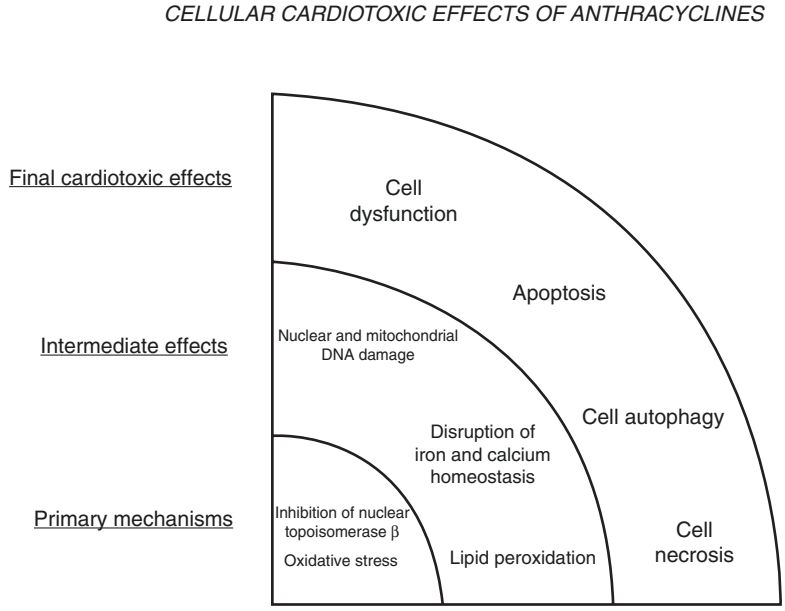

Fig. 7.2 Cardiotoxic effects of anthracyclines at the cellular level. (Modified from Tocchetti et al. [84])

CTX from target therapy refers mostly to four groups of drugs: (1) epidermal growth factor receptor 2 (HER2/ErbB2) inhibitors, (2) angiogenic inhibitors, (3) directed Abelson murine leukaemia viral oncogene homolog (ABL) inhibitors, and (4) proteasome inhibitors [22].

The main antihuman ErbB2 agent is Trastuzumab (T), a humanized monoclonal antibody against the extracellular domain of ErbB2. Trastuzumab treatment is an integral part of standard treatments for breast cancer with HER2 overexpression. T-CTX is represented mainly by LV systolic dysfunction and heart failure and, in contrast to anthracyclines, typically manifests during treatment and is usually reversible with trastuzumab interruption and/or treatment with HF therapies [23]. Otherwise treatment interruption has dramatic consequences, being associated with an increase in cancer recurrence [24].

Based on several large-scale trials of adjuvant therapy in breast cancer, the rate of trastuzumab-related cardiac dysfunction ranged from 7% to 34%, with HF (New York Heart Association [NYHA] classes III or IV) rates between 0% and 4% [25].

The concomitant or previous use of conventional chemotherapies, mainly anthracyclines but also antimetabolites and alkylating agents, substantially increases the cardiotoxicity of trastuzumab. Particularly, trastuzumab blocks the ErbB2 pathway mediated by neuregulin that plays an important role in mediating cell survival and functionality, and thus anthracycline-mediated damage may proceed uncontrolled [26].

Angiogenic inhibitors are used in patients with different solid cancers, but some of the VEGF inhibitors can cause reversible or irreversible cardiac side effects, particularly when used with or after conventional chemotherapies. Bevacizumab, pazopanib, axitinib, and particularly sunitinib can induce cardiac dysfunction in 3–15% of patients and symptomatic HF in 1–10% of patients [27–30].

ABL inhibitors have profoundly improved the prognosis of patients with several forms of chronic leukaemia and some forms of gastrointestinal stromal tumours [10]. Imatinib, a multitarget tyrosine kinase inhibitor binding ABL, but also c-Kit, and platelet-derived growth factor receptor, and the non-receptor tyrosine kinase sarcoma (SRC), is used in the treatment of Philadelphia chromosome-positive CML (Ph + CML) and GISTs. Despite initial concern about safety of imatinib [31], it is now demonstrated that it is a quite safe drug and heart failure/left ventricular dysfunction is not frequent

(0.2–2.7%) [10]. Dasatinib and nilotinib are two second-generation multitargeted TKIs that are used for the treatment of Ph + CML. Both dasatinib and nilotinib have rarely been associated with LV dysfunction and HF [20].

Bortezomib and carfilzomib are proteasome inhibitors of the first and second generation, respectively. They are used for the treatment of multiple myeloma and they can potentially cause cardiac dysfunction. In particular, carfilzomib is a more potent and irreversible proteosomal inhibitor, and preliminary data suggest a substantially higher risk of HF (up to 25%) [32, 33].

Radiotherapy

The estimated aggregate incidence of radiotherapy-induced cardiac dysfunction is 10–30% by 5–10 years post-treatment [34, 35]. However, due to the long delay between exposure and clinical manifestation of heart disease, and because patients usually receive concomitant cardiotoxic chemotherapy, the real incidence of radiation-induced cardiotoxicity is difficult to evaluate.

Systolic dysfunction is generally observed when radiotherapy is combined with anthracyclines. HF may also be aggravated by concomitant radiation-induced valvular heart disease (VHD) and coronary artery disease. Radiotherapy can induce marked interstitial myocardial fibrosis with lesions of variable volumes and distribution [34].

It is well established that there is a dose-dependent association between mediastinal RT and cardiovascular diseases such as coronary artery disease, valvular disease, and cardiomyopathy. Cumulative dose of radiation dose >30 Gy, high dose of radiation fractions (>2 Gy/day), and anterior or left chest irradiation are risk factors of radiotherapy-induced cardiac dysfunction [35]. Uncertain is the role of low-dose (<30 Gy) mediastinal RT [36–38].

Van Nimwegen et al. [39] showed that patients treated with 1–29 Gy of mediastinal RT had a non-significant increased risk of cardiomyopathy or HF as a first event. Similarly, studies [40, 41] of survivors of haematopoietic cell transplantation treated with total body irradiation found no association between lower-dose fractionated RT (12–13 Gy) and risk of HF as a first event.

Therefore, for patients who require mediastinal radiotherapy, lower radiation doses should be chosen and the use of more precise or tailored radiation fields with exclusion of as much of the heart as possible. These goals can be accomplished through the use of advanced techniques, including deep inspiration breath holding and intensity-modulated radiotherapy [42].

Beside dose, other risk factors of radiation-induced heart disease are young age (<50 years), concomitant chemotherapy (especially anthracyclines), presence of cardiovascular risk factors (i.e., diabetes mellitus, smoking, overweight, ≥ moderate hypertension, hypercholesterolemia), and pre-existing cardiovascular disease. High-risk patients are defined as those receiving anterior or left-side chest irradiation with ≥1 risk factors for RIHD [35].

Risk Factors for Cardiotoxicity

The risk of CTX is related both to the use of some anticancer agents (Tables 7.2 and 7.3) and to the presence of nontreatment-related modifier risk

Table 7.2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines

Risk factors
Cumulative dose
Female sex
Age
>65 years old
Paediatric population (<18 years)
Renal failure
Concomitant or previous radiation therapy involving the heart
Concomitant chemotherapy
Alkylating or antimicrotubule agents
Immunotherapy and targeted therapies
Pre-existing conditions
Cardiac diseases associating increased wall stress
Arterial hypertension
Genetic factors

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Table 7.3 Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors

Agent	Risk factors
Anti-HER2 compounds	
1. Antibodies Trastuzumab Pertuzumab T-DM1 2. Tyrosine kinase inhibitor Lapatinib	Previous or concomitant anthracycline treatment (short time between anthracycline and anti-HER2 treatment) Age (>65 years) High BMI >30 kg/mg2 Previous LV dysfunction Arterial hypertension Previous radiation therapy
VEGF inhibitors	
1. Antibodies Bevacizumab Ramucirumab	Pre-existing HF, significant CAD, or left side VHD (e.g., mitral regurgitation), chronic ischaemic cardiomyopathy Previous anthracycline
2. Tyrosine kinase inhibitors	
Sunitinib Pazopanib Axitinib Neratinib Afatinib Sorafenib Dasatinib	Arterial hypertension Pre-existing cardiac

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factors such as age, comorbidities, and compromised cardiac function [42].

Older Age

Cut-offs used to define older age at treatment have varied across studies, with most associations for increased risk seen in individuals who were ≥60 years of age at treatment. Several studies [43, 44] reported a significant and independent increased risk of cardiac dysfunction in older patients with cancer, treated with anthracyclines and/or trastuzumab when compared with younger patients with cancer.

Comorbidities

Modifiable risk factors such as smoking, hypertension, diabetes, dyslipidaemia, high alcohol intake, obesity, and sedentary habit were significantly associated with increased risk of cardiac dysfunction in patients with cancer treated with anthracyclines and/or trastuzumab [10, 40, 41, 43–51]. The presence of multiple modifiable risk factors (≥ two factors) was associated with the highest risk of HF [41]. Family history of premature CV disease (<50 years) also increases the risk of CTX [10].

Compromised Cardiac Function

Borderline low LVEF (50–54%), history of myocardial infarction, history of cardiac dysfunction, and presence of other cardiac comorbidities such as moderate valvular disease before starting anthracycline or trastuzumab therapy have been associated with an increased risk (3.6- to 11.8-fold) of cardiac dysfunction in three studies [43, 44, 49].

Individuals treated with potentially cardiotoxic therapies (e.g., anthracyclines, trastuzumab, or mediastinal RT) who have additional risk factors such as compromised cardiac function before treatment initiation, who have multiple cardiovascular risk factors (≥ two factors), or who are older (≥60 years) at the time of treatment should be considered as being at increased risk for developing cardiac dysfunction.

A limited number of studies have generated risk scores for different oncology patient cohorts [52, 53]. However, none of these risk scores has been validated prospectively, and clinical judgement is required when evaluating the risk at an individual level [10].

Risk assessment should include clinical history and examination and baseline measurement of cardiac function. Cardiac biomarkers (natriuretic peptides or troponins) may be considered in addition, using the same assay that will be used during follow-up measurements, to increase comparability. Finally, baseline risk assessment is often performed by the oncology team, but referral for cardiology evaluation is highly recommended in high-risk patients. High risk can be determined by both the number of risk factors and their severity. Patients at high risk for developing cardiotoxicity should be examined by a

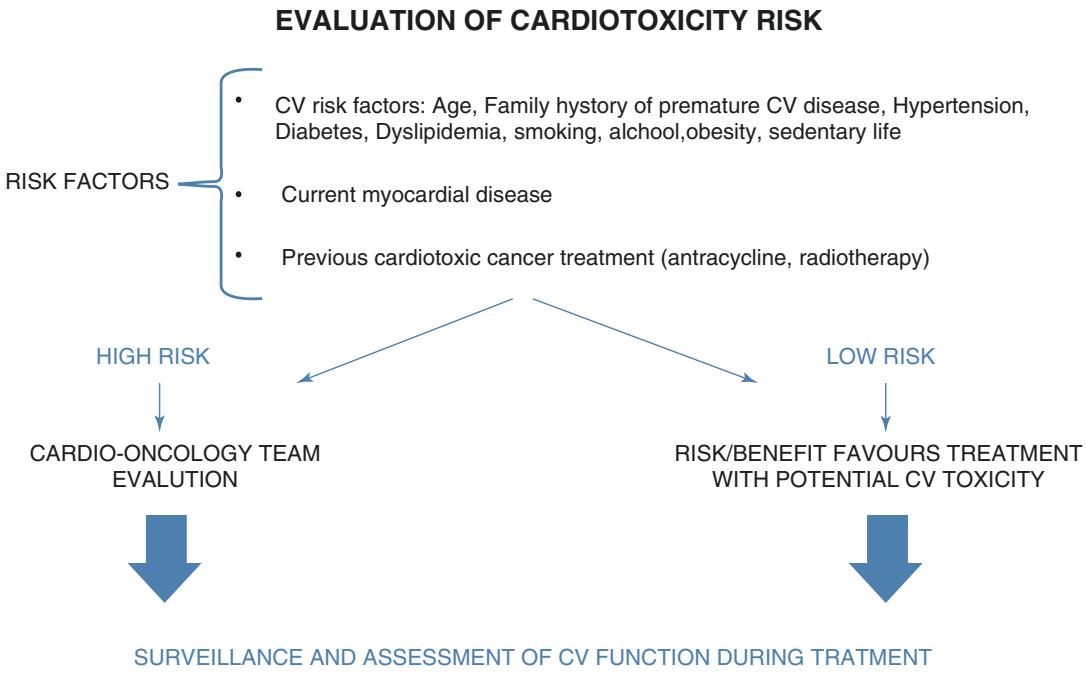

Fig. 7.3 Stratification of cardiotoxicity risk

cardiologist with expertise in this field or, if necessary, by a cardio-oncology specialist team (Fig. 7.3) [10].

Diagnosis of HF Induced by Cancer Therapies

Cardiac dysfunction developing during or after completion of cancer therapy is a growing health concern that should be addressed in a multidisciplinary setting, taking into consideration the costs as well as risks and benefits of early screening and prevention [10, 42].

Diagnostic tools to detect myocardial toxicity are electrocardiography (ECG), cardiac imaging (echocardiography, nuclear imaging, cardiac magnetic resonance [CMR]), and biomarkers (troponin, natriuretic peptides).

ECG is recommended in all patients before and during treatment [10]. Although ECG abnormalities are not specific, it is useful to detect any ECG signs of cardiac toxicity such as resting tachycardia, ST-T wave changes, conduction disturbances, QT interval prolongation, or arrhythmias.

Echocardiography is the method of choice for the detection of myocardial dysfunction before, during, and after cancer therapy [35, 54–63]. Evaluation of left ventricular systolic function can be performed by the measure of ejection fraction with 2D and, if available, with 3D echocardiography. To improve delineation of the LV endocardial borders, in patients with suboptimal acoustic window, the use of contrast echocardiography is encouraged. Cancer therapeutics-related cardiac dysfunction (CTRCD) is defined as a decrease in the LVEF of >10 percentage points, to a value below the lower limit of normal in repeated studies [10, 35, 49, 54–64]. However the definition of the lower limit of normal is controversial, being considered in many studies and by the recent ESC recommendation 50% [10] and by EACVI/ASE document 53% [54].

Ejection fraction is a not sensitive tool to detect subtle cardiac damage, and therefore to improve the accuracy in early diagnosis of cardiac dysfunction secondary to cancer therapy, the

use of deformation imaging is strongly recommended [10, 54]. Speckle-tracking echocardiography (STE) and peak systolic global longitudinal strain (GLS) appear to be the best measure [59].

Global systolic longitudinal myocardial strain (GLS) has been reported to precede and accurately predict a subsequent decrease in LVEF [65, 66]. A relative percentage reduction of GLS of >15% from baseline is considered abnormal and a marker of early LV subclinical dysfunction [54].

Besides echocardiography LVEF's evaluation can also be assessed by radionuclide angiography that is more reproducible but exposes the patient to ionizing radiation.

Finally, CMR is a helpful tool for the evaluation of cardiac structure and function with high accuracy. In addition, CMR is the unique technique that provides information on tissue characterization. In fact, chemotherapeutic agents can cause oedema and hyperaemia and even cellular necrosis and subsequent fibrosis [67]. Unfortunately this technique is not widely available.

In recent years, conventional and emerging biomarkers have been tested to detect anticancer drug-related cardiotoxicity (CTX). Encouraging results were obtained from studies on markers of myocardial damage, such as troponin and markers of myocardial wall stress, including circulating natriuretic peptides [68].

cTns are potentially the best characterized biomarkers for the evaluation of chemotherapy-induced CTX, because cTnI and cTnT are specific and reliable biomarkers for the recognition and quantification of myocardial injury [69, 70]. The cTns have been incorporated in the National Cancer Institute classification of CTX during cancer therapy, and their role has become particularly important, with evidence that their elevation may precede the perceptible changes observed in myocardial function. It has been shown that the increase in cTn allows discrimination between patients with a low risk of developing chemotherapy-induced CTX and those at high risk, which required more rigorous cardiac monitoring [71].

New elevation of serum troponin I detected with high-sensitivity assays in patients receiving anthracyclines and/or trastuzumab predicts subsequent LV dysfunction [58]. In patients with breast cancer, a small study demonstrated that the combination of high-sensitivity troponin with GLS might provide the greatest sensitivity (93%) and negative predictive value (91%) to predict future cardiotoxicity [65].

Based on these recent data, the EACVI/ASE expert consensus for multimodality imaging evaluation of adult patients during and after cancer proposed an integrated approach using cTn measurement and echocardiography, comprehensive of GLS for early detection of CTX [54].

The use of natriuretic peptides to detect HF is widely established, and increased levels can identify high-risk patients and guide therapy [72]. In the context of chemotherapy, B-type natriuretic peptide (BNP) and NT-proBNP may be useful, but their role in routine surveillance to define the high-risk patient is not established [73].

There is currently no clear evidence to withhold or interrupt chemotherapy or targeted therapies based on a new abnormal cardiac biomarker result, particularly with the application of increasingly sensitive assays or a reduction of GLS. However, an abnormal result identifies high-risk patients who should undergo a strict cardiological follow-up [10].

In fact, early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function [74].

Therapy and Cardioprotective Strategies

The goals of treatment in patients with HF, of whatever aetiology, are to improve their clinical status, functional capacity, and quality of life, prevent hospital admission, and reduce mortality.

Cancer patients presenting with clinical HF during or following cancer treatment should be treated according to current ESC guidelines for HF [1].

Neurohormonal antagonists (ACEIs, MRAs, and beta-blockers) have shown to improve survival in patients with HF and are recommended for the treatment of every patient with HF with

reduced EF (HFrEF) unless contraindicated or not tolerated.

When CTRCD occurs, ACE inhibitors (or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated [10]. Cardinale et al. [75] demonstrated that also in patients with very early damage, defined by an increased troponin I (TnI) value (>0.07 ng/mL) during treatment, early initiation of enalapril decrease the risk of cardiac dysfunction.

To reduce the risk of developing CTRCD, clinicians should screen for and actively correct modifiable cardiovascular risk factors (e.g., smoking, hypertension, diabetes, dyslipidaemia, obesity) in all patients receiving potentially cardiotoxic treatments and optimize treatment of concomitant cardiac disease, before starting treatment [10, 42]. Positive health-promoting behaviour, including lifestyle factors (healthy diet, smoking cessation, regular exercise, weight control), should be strongly advised. In particular, aerobic exercise is considered a promising non-pharmacological strategy to prevent and/or treat chemotherapy-induced cardiotoxicity [10].

In patients at risk to develop CTRCD, the benefit/risk ratio should be evaluated case by case by the cardio-oncology team, and if available, effective non-cardiotoxic drugs should be preferred.

Other potential options to reduce the risk of CTRCD include the use of preparations with a potentially less cardiotoxic profile (e.g., liposomal doxorubicin, continuous infusion,), reduction of the cumulative dose, and use of dexrazoxane, an intracellular iron-chelating agent that prevents anthracycline-mediated damage, indicated in Europe only for adults with advanced or metastatic breast cancer who have received high cumulative doses of anthracycline and would benefit from continued anthracycline-based therapy [10].

Prophylactic use of ACE inhibitors, beta-blockers, or ARBs for prevention of anthracycline-induced cardiotoxicity is an ongoing area of active investigation, and evidences are not univocal. With regard to beta-blockers, in one observational study [76] and in two randomized clinical trials [77, 78] using carvedilol and bisoprolol, the prophylactic use of beta-blockers decreased the risk of HF (however, in the MANTICORE study the primary endpoint of prevention of LV remodelling based on LV end-diastolic volume index with bisoprolol was not met). The Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) study demonstrated that the candesartan arm had a significant yet modest attenuation in the decline in LVEF when compared with metoprolol or placebo [79]. However, another placebo-controlled study failed to demonstrate a cardioprotective effect of candesartan in patients with breast cancer treated with trastuzumab [80]. Recently a prophilactic therapy to every patients did not show advantages compared to a troponin increased guided preventive strategy [81].

The Preventing Anthracycline Cardiovascular Toxicity With Statins (PREVENT) trial is an ongoing trial evaluating the efficacy of prophylactic atorvastatin (statin) to reduce the risk for cardiac dysfunction or HF.

Routine surveillance imaging may be offered during treatment in asymptomatic patients considered to be at increased risk of developing cardiac dysfunction. In these individuals, echocardiography is the surveillance imaging modality of choice that should be offered. GLS is a more sensitive tool to detect early cardiotoxicity than measurement of LVEF; however, currently cancer treatment should not be stopped, interrupted, or reduced in dose based on GLS reduction. Moreover despite supportive small studies exist, there is not yet evidence to guide cardioprotection through the detection of early signs of subclinical myocardial dysfunction by GLS surveillance [54, 59, 82]. We are waiting for the results of larger trial to confirm, if a GLS reduction guided therapy, that seems to be very rationale, is really superior to an EF guided one [83]. Genetic profiling of clinical risk factors and imaging, and clinical data may further improve patients who are at a high risk of developing.

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Coronary Artery Disease

8

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Introduction

Heart disease and cancer represent the two most common causes of death [1] in populations often exposed to the same risk factors; so, it is not surprising that many patients with heart disease have concomitant cancer, and many cancer patients are often affected by heart diseases.

Advancements in the treatment of cancer have improved the prognosis of patients with a wide range of malignancies [2], and in parallel, there has been increasing focus on cardiovascular effects of chemotherapeutic agents. In this context, the acute negative vascular effect of chemotherapeutic agents has become more relevant because of the latent effects of direct and indirect cardiovascular toxicity.

The expanding recognition and evidence base have produced strategies to mitigate the risk of heart failure and heart muscle toxicity induced by chemotherapy, particularly anthracyclines and HER2 receptor antagonists. In contrast, there is limited evidence base and mechanistic insight into the vascular complications, especially those pertaining to coronary arteries, associated with cancer chemotherapeutics.

Vascular complications of chemotherapy might occur as a result of an "off-target" drug effect or, importantly, as a result of a significant overlap between signaling pathways required for normal vascular function and those required for tumor growth. Vascular toxicity of chemotherapy often reflects endothelial dysfunction, with loss of vasorelaxant effects and suppressed anti-inflammatory and vascular reparative functions (Fig. 8.1). The propensity to develop cardiovascular complications in response to cancer therapy reflects the complex interplay between a patient's baseline cardiovascular risk and preexisting vascular disease such as coronary artery disease. In this regard, chest radiotherapy, which is commonly used to treat malignancies such as breast cancer and Hodgkin's disease, has been shown to accelerate the atherosclerosis process, resulting in early-onset coronary artery disease.

For these reasons, it might be appropriate to review the oncological therapeutic strategies in patients at high risk of vascular complications, whereas in others, the potential for vascular

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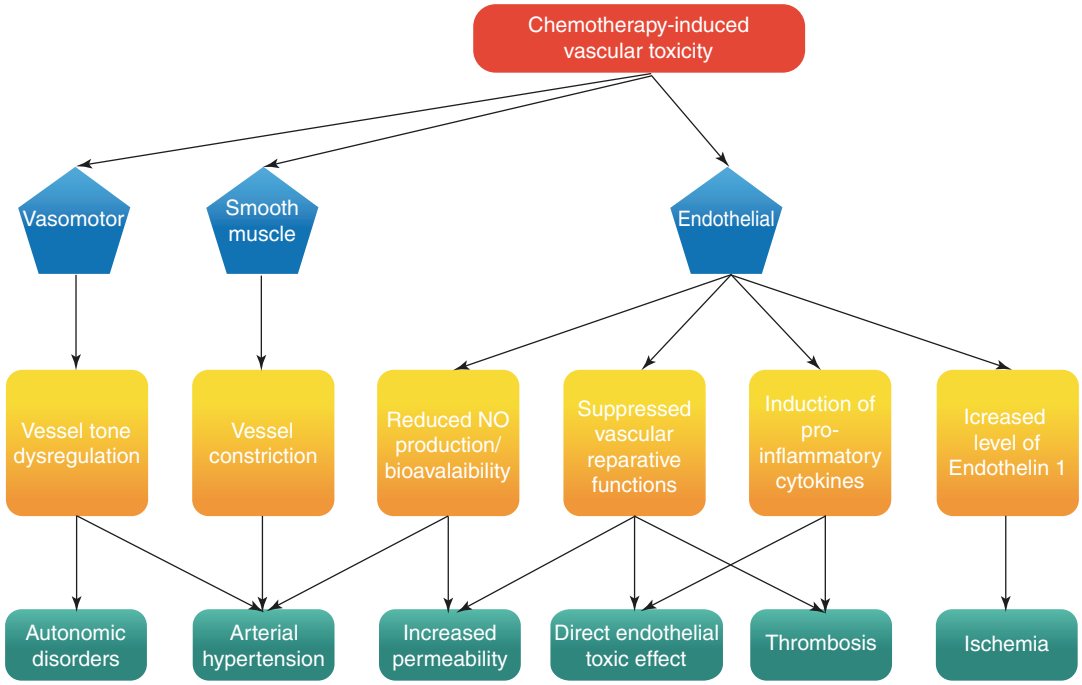

Fig. 8.1 The main mechanism of chemotherapy-induced vascular toxicity. (Adapted from Soultati et al. [13])

toxicity might be safely managed without reducing the net benefit from chemotherapy and radiotherapy [3].

A better understanding of the risk and its stratification is necessary for efficient treatment of patients at high risk of developing coronary artery disease or already affected by coronary artery conditions.

Coronary Damage Induced by Chemotherapy and Radiotherapy

Pathophysiology of coronary damage may vary depending on the specific chemotherapy used. Many chemotherapies proved to exert vascular toxicity.

For most agents, vascular toxicity often reflects endothelial dysfunction, with loss of vasorelaxant effects and suppressed anti-inflammatory and vascular reparative functions. These effects might initiate and further perpetuate the development of hypertension, thrombosis, and atherogenesis. Moreover, in addition to the procoagulant effect of cancer per se, most agents further enhance platelet activity by decreasing endothelial nitric oxide (NO) bioavailability (Fig. 8.1) [3].

Alkylating agents were among the first drugs shown to induce these cardiac complications. Platinum-based compounds like cisplatin were shown to be associated with acute and late cardiovascular side effects, including hypertension, myocardial ischemia and infarction, thromboembolism, and cerebrovascular disease [3]. Over a median follow-up of 14 years, cisplatin-based chemotherapy for metastatic testicular cancer had been associated with a sevenfold increased risk of a major cardiac event (6% of patients) [4]. Potential mechanisms that might contribute to thrombus formation include endothelial cell damage and dysfunction provoking a hypercoagulable state with platelet activation, adhesion, and aggregation, increased von Willebrand factor level, and reduced NO bioavailability [3]. Treatment with cisplatin has been related to long-lasting cardiotoxicity with an increased risk of myocardial infarction afterward. In these patients,

the plasma levels of cisplatin remain measurable for up to 20 years after the completion of therapy and cause cumulative dysfunction of endothelial cells [5]. Therefore, in this case, long-lasting pharmacological presence of circulating cisplatin correlates with molecular mechanisms of damage such as endothelial dysfunction and clinical events like acute coronary syndromes.

Cardiac toxicity of fluoropyrimidines is the second most common cause of chemotherapy-induced cardiotoxicity [6]. Although most frequently 5-fluorouracil causes angina-like chest pain, in rare cases myocardial infarction, arrhythmias, ventricular tachycardia, heart failure and cardiogenic shock, and QT prolongation with torsades de pointes have been reported [7, 8].

Extreme variations in the incidence of cardiac toxicity associated with 5-fluorouracil (5-FU) have been reported [9]. The pathogenic mechanism of cardiotoxicity associated with 5-FU and capecitabine has been linked to coronary thrombosis, with arteritis and vasospasm proposed as possible mechanisms. Certain metabolites of 5-FU have been shown to be associated with cardiotoxicity. Thymidine phosphorylase is an enzyme involved in the conversion of capecitabine into 5-fluorouracil and of 5-FU into its active metabolites; this enzyme is an angiogenic factor [10, 11] whose expression is upregulated in atherosclerotic plaque and during acute coronary syndromes [12]. The detrimental effect of the drugs could also be mediated by endothelial impairment, with increased levels of endothelin-1 leading to vasospasm and ischemia (Fig. 8.1).

5-FU can also directly damage vascular endothelium, reducing endothelial NO synthase activity and endothelium-independent vasoconstriction via protein kinase C. Coronary endothelium is particularly susceptible to these effects, leading to a Prinzmetal-type angina phenomenon [13].

Although 5-FU exerts acute effects on the coronary arteries in terms of vasospasm and possibly thrombus formation, it has not been associated with the development of accelerated coronary atherosclerosis. However, experimental studies have also implicated endothelial and myocardial cell apoptosis [13], although 5-FU causes a dose-dependent increase in red blood cell viscosity and reduced blood flow velocity, which predispose to thrombus formation. Preexisting coronary artery disease remains a risk factor for 5-FU-related vasospastic angina, which most likely explains the observation that vasospasm tends to occur at sites of thrombus and plaque formation [14]. Repeated challenge with 5-FU or capecitabine tends to result in recurrent symptoms, and alternative agents should be used when toxicity has occurred.

Taxanes and vinca alkaloids exert their antineoplastic effect by altering the cellular microtubule mass, which represents one of the most successful targets for chemotherapy agents. Taxanes have significant anti-angiogenic properties and cause disruption of the cytoskeleton and endothelial cell function [13]. At low doses, they block critical signaling pathways and prevent cell motility and cell-cell interactions [13, 15]. At higher doses, they cause microtubule deficiency, with endothelial cell detachment and apoptosis. Paclitaxel attenuates vascular smooth muscle cell migration and halts endothelial cell proliferation [13]. It might also have pro-thrombotic effects through enhanced endothelial tissue factor expression via selective activation of c-jun kinase [13, 16].

The vascular side effects of taxanes are amplified when these drugs are used in combination with angiogenesis inhibitors. The combination of bevacizumab with paclitaxel in patients with advanced breast cancer increases the rate of severe thrombotic events from 1.5% to 2.1% [17].

The vinca alkaloids vincristine and vinblastine are tubulin binders that induce cell death and are primarily used in the treatment of leukemia and lymphoma. Their main cardiovascular side effects are myocardial ischemia and infarction, which tend to occur during or shortly after therapy and might therefore be related to coronary artery vasospasm as a result of cellular hypoxia [14].

In the recent years, vascular endothelial growth factor inhibitors (VEGF-Is) have become the cornerstone of therapy for a wide variety of solid tumors and hematological malignancies. Hypertension is the most common cardiovascular complication associated with VEGF-Is [18].

However, the interruption of VEGF signaling is associated with the development of vascular toxicity and clinical sequelae such as acute coronary syndromes, stroke, venous thrombosis, and thromboembolism [13], [14]. The risk of arterial thrombosis appears to be greater than that of venous thrombosis [19]. Bevacizumab is associated with a 2.1-fold increased risk of high-grade cardiac ischemia [20], sorafenib is associated with a 3% incidence of myocardial ischemia or infarction [21], and a study of sunitinib in patients with advanced clear-cell renal carcinoma showed a 1% incidence of myocardial infarction [19]. Although the absolute increase in risk is relatively small (0.8% and 1.8% for myocardial infarction and arterial thrombosis, respectively), it is clinically important, particularly for those with preexisting risk factors or vascular disease. Patients with previous coronary artery disease are at a particularly high risk of developing vascular complications [22], and it might be reasonable to consider screening patients for preexisting coronary artery disease before commencing anti-angiogenic treatment.

Additionally, tyrosine kinase inhibitors developed for use in the treatment of hematologic malignancy, including ponatinib, nilotinib, and dasatinib, are associated with a particularly high incidence of acute arterial thrombosis. This is especially evident for ponatinib [22], which was associated with a nearly 12% incidence of arterial thrombotic events at 2 years, with most such events occurring as an acute thrombotic process [22]. Mechanisms underlying the high incidence of acute arterial events associated with ponatinib and nilotinib remain unclear.

Finally, chest radiotherapy, which is commonly used to treat malignancies such as breast cancer and Hodgkin's disease, is, like many types of chemotherapy, associated with cardiovascular complications, including coronary artery disease. Mediastinal radiation therapy was shown to accelerate the atherosclerosis process, resulting in early-onset coronary artery disease [23].

Endothelial inflammation accelerated by radiation exposure potentiates intimal damage and promotes the development of atherosclerotic plaques in coronary vessels [24]. Several small animal models suggest that the development of cardiovascular disease induced by radiation is multifactorial and depends on the type of radiation particle, location of radiation exposure, and amount of tissue exposed [25].

Coronary artery disease may develop 5–20 years after radiation exposure and initially tends to be asymptomatic [23].

Coronary Artery Disease as a Risk Factor Before Cancer Therapy

Coronary artery disease and malignoma are associated in several cancers, e.g., lung and breast cancer and lymphoma [3, 26]. Cardiovascular risk factors like obesity, hyperglycemia, hypertension, and hyperlipidemia mediate inflammation processes in the circulation system, resulting in arteriosclerosis mainly caused by lipid storage [27]. Additional sources of inflammation like viral infections, allergen exposure, radiation, toxic chemicals, alcohol consumption, ongoing tobacco use, and chronic and autoimmune diseases facilitate the progression of endothelial dysfunction and vessel damage in the arterial circulation, inducing plaque formation, plaque rupture, and intra-arterial thrombosis. It is known that statins can prevent ischemic cardiac events in coronary artery disease and improve prognosis by lowering the cholesterol level and producing anti-inflammatory effects. Actual positive results of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) will support the existence of interactions between coronary artery disease and cancer [28]. Canakinumab, an inhibitor of a pro-inflammatory cytokine interleukin-1β, seems to alleviate the progression of atherosclerosis and reduce the incidence of cancer.

It is obvious that the presence of coronary artery disease prior to the diagnosis of cancer is a potential life-threatening factor for the patients. The activation of cytokines and chemokines such as growth factors and heparanase in several cancers induces thrombus formation known as paraneoplastic syndrome, which can cause acute myocardial infarction via hemo-

static activation [29]. Thus, cancer patients with undetected coronary artery disease, especially in the presence of thrombocytosis and hyperfibrinogenemia, are predisposed to major cardiac events during chemotherapy [30].

A history of myocardial infarction demonstrates the presence of coronary artery disease in patients with cancer. Depending on the extent of infarction, left ventricular dysfunction may be observed. The severity of left ventricular dysfunction is crucial for an individual patient with cancer because left ventricular ejection fraction remains the most important parameter for the decision whether to perform a cardiotoxic chemotherapy. It is well-known that cancers of different internal organs tend to occur soon after percutaneous coronary interventions, interfering with potential surgical interventions in the presence of dual antiplatelet therapy, which indicates that myocardial infarction could be a primary symptom of neoplasms caused by hemostatic activation.

Because of the paraneoplastic syndrome, this cohort of patients is at high risk of myocardial reinfarction. For a cancer patient with severe coronary artery disease, the pivotal decision of whether to initiate chemotherapy, which could represent the only curative treatment, is dependent upon the results of risk stratification by the oncologist. Typically, there is no optimized interdisciplinary approach to monitor the residual myocardial function in short-term echocardiographic investigations with modern modalities, which would allow detecting potential cardiotoxicity at an early stage, enabling proper treatment, and guiding chemotherapy by monitoring signs of cardiotoxicity.

Chronic heart failure due to end-stage coronary artery disease at the time of cancer diagnosis can also be a substantial limitation for chemotherapy. Worsening of heart failure is often compounded by the necessity of induced hypervolemia to increase the renal clearance of destroyed tissue products due to the biological degradation of tumor cells. On the other hand, cardiological treatment of chronic heart failure with volume restriction and diuretics administration often induces renal failure, which further limits chemotherapy.

Management of Chest Pain and Coronary Syndromes Induced by Chemotherapy and Radiotherapy

Chest pain in patients with cancer could have various etiologies, including pulmonary embolism, pericardial irritation, and myocardial ischemia. The latter could be triggered by a number of chemotherapeutic agents, of which, as previously described, the most typical is 5-FU, which causes chest pain in up to 18% of patients. Chest pain may have a prompt onset and be related to an alteration in vascular reactivity [31, 32]. The types of presentation can include effort angina and positivity to a noninvasive stress test [33] but also resting and variant angina. As previously described, this is related to the fact that these drugs primarily alter molecular signaling pathways that control vascular smooth muscle cell tone and induce vasoconstriction [34]. Taxanes can also induce chest pain, with incidence of up to 4% [35]. Similar to 5-FU, vasoconstriction has been considered to be a key mechanism.

Cisplatin, alone or in combination with bleomycin and vinca alkaloids, can provoke chest pain with incidence as high as 40% [36]. Endothelial dysfunction and altered vasoreactivity are the key mechanisms for these drugs [37].

VEGF-Is are another class of drugs that could induce vasoreactivity impairment with angina in up to 15% of patients. Accelerated atherosclerosis of coronary arteries has been observed in patients receiving sorafenib, progressing from a normal coronary angiogram to critical coronary sub-occlusion over the course of only 4 years [38].

Patients with cancer can also develop signs and symptoms of myocardial ischemia as a consequence of coronary artery compression by various cardiac and noncardiac tumors [39]. Malignant tumors, like mediastinal tumors such

as lymphoma, can cause coronary compression that may lead to myocardial infarction [40].

Moreover, the toxic effects of chemotherapy on fast-dividing cells such as blood, gonadal, and endothelial cells induce anemia unrelated to immunosuppression, infertility, and gastrointestinal conditions.

Anemia can provoke typical angina because of a mismatch of energy demand and energy supply. Myocardial ischemia can be induced by concomitant anemia in combination with physiological sinus tachycardia. Typical angina predominantly occurs in patients with epicardial narrowing of the coronaries, where the anemia is more severe owing to pronounced hypoperfusion in post-stenotic areas. Blood transfusion as well as volume overload can be a challenge in patients with left ventricular dysfunction due to previous myocardial infarction, severe coronary artery disease, and heart valve diseases.

The management of these clinical syndromes is not outlined in guideline-based recommendations. Assessment of the baseline cardiovascular history and risk is the key first step, and any potentially modifiable risk factor and disease state should be optimized before proceeding with any potentially cardiotoxic therapy.

Given the property of several agents to cause coronary vasoconstriction, high-risk patients should be tested for peripheral vasoreactivity and, in some cases, undergo cardiac stress tests or coronary angiography.

If chest pain occurs, administration of nitroglycerin and calcium channel blockers is the best initial diagnostic and therapeutic step. A more comprehensive and definitive assessment is usually advisable for patients at risk of developing progressive atherosclerosis. The goal is to facilitate the continuation of chemotherapy while managing and mitigating cardiovascular disease risk and side effects.

The general management of chemotherapy-induced syndromes, which could induce myocardial ischemia, also includes the treatment of anemia by blood transfusion and normalization of pulse frequency to extend diastole, thereby improving coronary perfusion. This approach is equivalent to the conservative treatment of stable angina using beta-blockers, nitrates, molsidomine, calcium channel blockers, ivabradine, or ranolazine. The additional interventional treatment of significant coronary artery stenosis in patients with cancer is crucial because of possible hemostatic activation in paraneoplastic syndrome. Thus, conservative treatment of coronary artery disease seems to be preferable in patients receiving chemotherapy to prevent intracoronary thrombosis after percutaneous angioplasty with or without stent implantation.

Hypo- and hypertension due to paraneoplastic activation and various treatment regimens must be treated individually according to the underlying causes. Coronary microvascular dysfunction can be often observed during chemotherapy. Myocardial edema, vascular inflammation, and multiple drug-induced interactions can explain the deterioration of microvessel function.

A special scenario is the obstruction of coronary arteries—mainly in the ostial regions—after chest radiation, e.g., in mediastinal, breast, and lung tumors in late stages after successful cancer treatment. These stenoses are often less elastic owing to a diffuse scarring process. Thus, interventional treatment must be performed with high-pressure balloons and stenting because of severe retractile forces of these coronary segments.

Acute coronary syndromes, from unstable angina to myocardial infarction and even sudden cardiac death, can also develop in patients who have cancer. Several agents can modify coronary vasoreactivity, leading to resting or unstable angina. The intensity and duration of vasoconstriction can even provoke myocardial infarction and arrhythmia.

Acute coronary syndromes could also be related to consequences of well-established types of plaque complications. Some chemotherapeutic agents are known to exert endothelial cell damage, with patients with cancer being more susceptible to plaque erosion. This mechanism is supported by experimental studies that have shown the induction of endothelial damage to the point of apoptosis and stimulation of thromboxane production, platelet activation, and platelet aggregation [41, 42].

Coronary thrombosis has been demonstrated by angiography without any underlying atherosclerosis [41, 43]. This risk seems to be particularly high in patients ≥65 years of age or with a previous arterial thromboembolic event [44].

Patients with cancer are also at risk of coronary artery occlusion due to thromboembolism, which may occur because of their predisposition to a procoagulant state [45, 46]. Another atypical mechanism of acute coronary syndrome is spontaneous coronary artery dissection [47, 48].

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

Nitroglycerin to relieve any possible coronary vasoconstriction should be the first treatment in cancer patients who develop signs and symptoms of myocardial ischemia. Coronary angiography should be performed to exclude any other concomitant complications that could account for the acute coronary syndrome presentation (especially in the presence of high-risk clinical conditions like refractory angina or malignant arrhythmias) and to guide treatment decisions.

In most patients with cancer, this approach can be employed safely despite other complications like anemia, thrombocytopenia, and coagulation abnormalities.

Alternative management strategies could employ noninvasive stress testing or advanced vascular imaging techniques like intravascular ultrasound and optical coherence tomography.

Antithrombotic agents may be useful during treatment with VEGF-Is. In patients treated with bevacizumab, administration of aspirin reduced the risk of ischemic events, especially in older individuals (≥65 years) and those with history of an arterial thrombotic event (12.5% versus 22.9%), although it was associated with an increased risk of bleeding [44].

Management of Coronary Disease in Patients with Cancer

Cancer patients with coronary disease present particular challenges that directly impact the management of the coronary disease, both stable and acute. The frequent need for surgery in these patients necessitates avoiding coronary artery stenting or any percutaneous coronary intervention for the management of chronic stable angina because this would delay surgery or create a risk of stent thrombosis during surgery. Moreover, the possibility of thrombocytopenia at some point in the disease course and the increased susceptibility to thrombosis represent a great challenge in these patients.

A problem specific to patients with cancer is that the surgery usually cannot be postponed for more than a month, and, additionally, chemotherapy creates a risk of thrombocytopenia in the near future. These considerations have a great impact on the decision whether to perform revascularization. Perioperative evaluation and management depend on the urgency of the surgery, stability of the coronary disease, risk associated with the surgery, and functional capacity of the patient. For the cancer surgeon, breast, endocrine, reconstructive, gynecologic, and minor urologic operations are considered low risk, whereas abdominal and urologic operations, as well as most transplantations, are considered intermediate risk [49]. With careful management, patients with stable coronary disease should be able to tolerate cancer surgery without extensive evaluation of exercise tolerance. Revascularization should be an exception rather than the rule.

Another major problem in patients with cancer and coronary artery disease is the noted interaction between drugs used to treat coronary disease and cancer.

Statins are essential in the treatment of both acute and chronic coronary artery disease. A potential interference between paclitaxel and CPY2C8 pathway, a key pathway in the metabolism of simvastatin, has been documented [50]. Lately, there has been considerable interest in the possibly useful interaction between statins and cancer. Of interest are the noted anti-inflammatory effects of statins and their possible effects on angiogenesis [51, 52]. It has also been suggested that statins may magnify the effect of cancer therapeutics as well as possibly reduce multidrug resistance [53]. Moreover, a possible decrease in thromboembolism in patients with cancer receiving statins has been suggested [54]. Finally,

animal studies and a human trial suggested that antithrombotic therapy with prasugrel, a new thienopyridine introduced for the treatment of acute coronary syndrome, may enhance cancer metastasis [55].

In general, evidence of interaction between drugs used to treat coronary disease and cancer is still scarce, necessitating further research.

Management of Chemotherapy in Patients with Chronic Coronary Disease

The clinical diagnosis of coronary artery disease is normally based on symptoms like cardiac dyspnea, angina, or palpitations during rest or stress-induced ischemia. The ischemic cascade after initiation of hypoperfusion is characterized by pathophysiological and clinical features. Thus, the first cardiac alteration is dysfunction of relaxation, followed by reduction of regional contraction and wall motion abnormalities, which are the first sign of stress-induced ischemia in conventional stress echocardiography. Electrocardiographic changes and angina are observed later with increasing myocardial ischemia. According to the current guidelines and recommendations, patients with acute myocardial infarction and unstable angina should immediately undergo coronary angiography and interventional treatment [56].

Symptoms like acute chest pain can be caused by acute myocardial infarction, which is defined as myocardial injury and necrosis indicated by a significant increase of troponin level. Myocardial infarction is clinically defined as ongoing chest pain and angina after acute treatment and can present as ST- or non-ST-segment elevation infarction. Patients with acute myocardial infarction need to undergo interventional therapy when possible [57]. The imaging criteria of acute myocardial infarction are evidence of new loss of viable myocardium tissue and/or new regional wall motion abnormalities [58]. In a new patient, detected wall motion abnormalities must be classified as acute. However, in the absence of non-ischemic causes, loss of viable myocardium, with thinned tissue that fails to contract, can indicate a prior myocardial infarction. Myocardial infarction is normally caused by acute intracoronary thrombosis after plaque rupture, which can be detected by angiography of the epicardial coronary arteries. However, myocardial infarction can also occur in the absence of obstructive coronary artery disease.

Angina prior to infarction is classified as unstable or stable. The first occurrence of typical angina and angina combined with a new left bundle branch block belong to unstable angina, which is also characterized by increasing severity during consecutive episodes [56]. Cardiac imaging normally documents regional wall motion abnormalities in unstable angina, which corresponds pathophysiologically to hibernating myocardium. Owing to the risk of aggravation and plaque instability, invasive coronary angiography is indicated. However, in the presence of malignoma, the risks of bleeding and stent thrombosis need to be balanced when devising subsequent interventional treatment.

Stable angina includes stress-induced angina and wall motion abnormalities in patients with known and previously treated coronary artery disease or with known cardiovascular risk factors. Interventional therapy is only feasible in the presence of main stem stenosis, severe proximal stenosis of the left anterior descending artery, and severe stenosis in multiple coronary vessel disease with concomitant vessel occlusion [59]. It was shown that interventional therapy is not better than optimal medical treatment in coronary single-vessel disease of the right coronary artery or circumflex branch and in distal coronary multivessel disease [60]. Thus, the efficiency of interventional therapy has to be carefully balanced against the risk of post-interventional thrombotic complications due to potential hemostatic activation, especially in patients with cancer. Stable angina can also be caused by nonobstructive coronary artery disease such as takotsubo cardiomyopathy, repetitive coronary microembolism, coronary spasm, and coronary microvascular disease.

The modalities for diagnosis of coronary artery disease and myocardial damage are echocardiography, cardiac magnetic resonance tomography, myocardial scintigraphy, and nuclear

imaging modalities [61, 62]. Especially for repetitive follow-up investigations, transthoracic echocardiography, including tissue velocity imaging and speckle tracking, is the most often used imaging modality in the clinical setting [61].

Early alterations due to chemotherapy-induced myocardial damage can be reflected by impairment of diastolic left ventricular function [63]. The echocardiographic assessment of diastolic dysfunction includes the determination of left atrial size and emptying function as well as A-wave velocity and A-wave duration of the retrograde flow in the pulmonary vein. An increase of the retrograde A-wave velocity of more than 35 cm/s and a larger duration of the retrograde flow during A-wave in the pulmonary vein than of the orthograde trans-mitral flow are indications of impairment of diastolic filling capacity of the left ventricle.

Cardiotoxicity affecting left ventricular myocardium is still detected based on reduction of left ventricular ejection fraction, which is a very unreliable parameter owing to the high interobserver variability in conventional bidimensional echocardiography. To increase accuracy, dobutamine stress echocardiography combined with tissue Doppler velocity imaging during diastole as well as cardiac magnetic resonance tomography were proposed as an alternative approach. 3D transthoracic echocardiography was also shown to yield more reproducible values of left ventricular volumes and ejection fraction. However, actual echocardiographic techniques like deformation imaging with tissue Doppler and speckle tracking provide better insights into myocardial alterations due to cardiotoxicity, especially during subclinical stages of the disease [64].

Global longitudinal peak systolic strain seems to be a more robust parameter than left ventricular ejection fraction, which makes it more suitable for detecting myocardial cardiotoxicity in follow-up investigations. Other indicators of left ventricular deformation such as radial and circumferential strain are promising options. Analysis of the dynamics of cardiac rotation was shown to be able to detect cardiotoxicity earlier than analysis of left ventricular ejection fraction and global longitudinal peak systolic strain [65].

The monitoring of coronary damage and detection of microcirculatory dysfunction can be performed via the assessment of coronary flow reserve during vasodilator stress [66, 67]. The endothelium-dependent vasomotion can be analyzed during adenosine or dipyridamole stress. Whereas the flow pattern of the epicardial coronary arteries, maximum velocities >4 m/s, and reduced coronary flow reserve (<2) are markers of severe epicardial stenosis, reduced coronary flow reserve in the presence of normal flow patterns can be interpreted as coronary microcirculatory dysfunction [68, 69]. In patients undergoing chemotherapy, non-specific signs of myocardial alterations can often be identified based on the phenomenon of global or regional postsystolic radial shortening. This contraction pattern can be induced by edema or inflammation, which also induces microvascular dysfunction. Monitoring of the microvascular properties during the treatment with diuretics and anti-inflammatory agents can be performed by measuring coronary flow reserve during vasodilator stress to document therapeutic effects. In addition, myocardial contrast echocardiography may be able to measure myocardial perfusion, but this approach is not yet established in routine clinical practice [61].

Strategies to prevent myocardial damage induced by chemotherapy imply accurate risk stratification and early detection of cardiotoxicity [70]. It is obvious that all available diagnostic tools, including electrocardiography, echocardiography, nuclear imaging, cardiac magnetic resonance tomography, and analysis of biomarkers, should be used. Cancer treatment in patients with coronary artery disease can induce myocardial ischemia, myocardial infarction, and ischemia-induced arrhythmias via several different mechanisms. Cancer treatment can provoke syndromes due to coronary artery disease, e.g., via anemia. Cardioprotection in patients undergoing chemotherapy and measures to prevent cancer therapy-induced myocardial damage include interrupting the chemotherapy or reducing the dosage to allow recovery of myocardial function and administration of agents such as beta-blockers, especially carvedilol, angiotensin-converting enzyme inhibitors, and angiotensin

receptor blockers, which are typically used in the therapy of chronic heart failure. Antioxidants can potentially have an additional cardioprotective effect, which is supported by the recent data of the CANTOS trial [29].

Conclusions

Coronary artery disease is a major risk factor and obstacle in the treatment of cancer. The undesired property of cancer therapy to induce cardiovascular impairment reflects the complex interplay between a patient's baseline cardiovascular risk and preexisting cardiovascular disease. Baseline cardiovascular assessment is vital for the selection of appropriate chemotherapy, and preexisting cardiac disease must be treated aggressively.

Several chemotherapeutic agents are known to trigger ischemic heart disease, and as it has happened for myocardial cardiotoxicity, more attention should be directed to early recognition and prevention of cardiac vascular toxicity.

An interdisciplinary approach based on the principles of oncology and cardiology should extend chemotherapeutic options for patients with coronary artery disease and reduced left ventricular function provided that comprehensive, accurate, and frequent follow-up, mainly by echocardiography, is performed.

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9 Peripheral Artery Disease and Stroke

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Peripheral Artery Disease

Incidence and Pathophysiology

Peripheral artery disease (PAD) can occur as complication secondary to anticancer treatment, with an incidence of up to 30% [1]. BCR-ABL tyrosine-kinase inhibitors (TKIs), used for the treatment of chronic myeloid leukemia (CML), are the main antineoplastic drugs involved in the development of PAD being responsible of the development of vascular adverse events. Due to the emerging resistance against imatinib, considered a "gold standard" of treatment for patients with newly diagnosed CML, more effective TKIs, including nilotinib, dasatinib, bosutinib, and ponatinib, have been developed and are successfully used in daily practice [2–5]. Their superior efficacy with a major antileukemic activity is, however, accompanied by the development of adverse effects, due to the expression of several targets also in non-hematopoietic cells.

Vascular damage is an emerging type of clinically relevant complications in patients receiving second- or third-generation BCR-ABL1 TKIs and includes coronary artery disease, cerebral ischemic disease (stroke), and PAD [6–9]. The exact incidence of vascular complications is still debated, but according to most studies, emerging data are the following: (1) the frequency of vascular adverse events increases over time; (2) it is higher in patients treated with higher doses of nilotinib (800 vs 600 mg daily) or ponatinib (45 mg vs 30 or 15 mg daily); and (3) there is a certain correlation between preexisting cardiovascular risk factors (CVRF) and vascular complications [10–13]. The various TKIs have distinct vascular safety profiles, most likely due to each compound's different kinase inhibition profiles and non-kinase targets. Even if nilotinib and ponatinib are the BCR-ABL TKIs more involved in the development of vascular damage, recent data suggest that vascular disease can also occur in CML patients treated with dasatinib or bosutinib, but with a lower incidence (<5% of patients) [14, 15]. On the contrary, the incidence of vascular complications in patients treated with imatinib appears to be low, interesting less than 1% of patients [13]. Imatinib was found to

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improve the fasting blood glucose level; thus, it can explain a possible protective effect of imatinib on the formation of atherosclerotic plaque and the related cardiovascular diseases [16].

When evaluating the risk of PAD development in such patients treated with BRC-ABL TKIs, different factors have to be considered (Table 9.1). First of all, the presence of pre-existing CVRF, such as hypertension, diabetes mellitus, dyslipidemia, smoke, and pre-existing vascular disease has to be investigated. Another relevant factor affecting the development of vascular complication is the dose of TKIs, with increased risk at higher doses. Therefore, lowering the dose of drug administered can reduce the incidence of vascular adverse effects. Moreover, shorting the time of exposure to these TKIs can lower the risk of PAD and stroke. In addition, also the sequential use of certain TKIs, such as nilotinib and sorafenib, increases the risk of vascular complications; thus, it has suggested to avoid it if possible [10, 17].

Table 9.1 Clinical risk factors contributing/predisposing to the occurrence of VAE in CML patients treated with nilotinib or ponatinib

Risk factors
Predisposing genetic factors:
Genetic variations predisposing to the occurrence of hypercholesterolemia or the development of diabetes mellitus
Age and sex:
Advanced age
Males > females
Acquired somatic mutations:
Clonal age-related hematopoiesis
Clonal hematopoiesis of indeterminate potential (may predispose for development of CML as well as development of VAE)
Lifestyle-related risk factors:
Nicotine consumption
Overweight/obesity
Refused/irregular drug intake
Preexisting overt comorbidities:
Arterial hypertension
Hypercholesterolemia
Diabetes mellitus
Thrombosis, stroke, other arteriopathies
Dose of TKI and TKI sequence:
Higher doses of nilotinib (800 mg/day) or ponatinib (45 mg/day)
Sequential exposure to nilotinib and ponatinib
Time of TKI therapy:
Longer exposure to nilotinib or ponatinib

Adapted from Valent et al. [10]
VAE vascular adverse event, *TKI* tyrosine-kinase inhibitor, *CML* chronic myeloid leukemia

Finally, genetic risk factors may predispose for vascular occlusive disease in patients treated with nilotinib or ponatinib; however, only little is known about these factors [18]. Due to the relative rapid onset of vascular complications in patients under TKI treatment (within 12 months after starting therapy), it has been hypothesized a direct effect of drugs on vascular cells [6]. Some studies have postulated that TKIs can induce a vasospasm or rapid stenosis formations in arteries; however, now, there is a strong evidence about pro-atherogenic effects on endothelial cells [9, 19]. It was demonstrated that nilotinib and ponatinib may promote the expression of pro-atherogenic surface adhesion receptors on human umbilical vein-derived endothelial cells in vitro [10, 20]. Moreover, neo-angiogenesis plays a pivotal role in vascular repair processes which are fundamental in favoring survival and recanalization of affected arteries.

Both nilotinib and ponatinib have an anti-angiogenic activity and inhibit proliferation and survival of human endothelial cells in vitro [20]. In addition, nilotinib treatment resulted in an unbalanced pro−/anti-inflammatory network in a clinical cohort of patients who received either imatinib or nilotinib, which could lead to a pro-atherothrombotic predisposition, another possible driver of vascular complications [20]. It was also reported that nilotinib might induce metabolic disorders, in particular increased fasting glucose and cholesterol levels, associated with the increased risk of developing vascular occlusive events [21–23].

Nilotinib treatment is also associated with hypothyroidism, which can affect lipid and glucose metabolism. Even if the exact cellular interactions and mechanism underlying nilotinib-induced hyperglycemia and hypercholesterolemia remain unknown, these metabolic changes can favor the

development of atherosclerosis in patients with CML.

Finally, all this spectrum of actions exerted by BRC-ABL TKIs can explain the elevated risk of PAD developments in patients treated with these drugs, especially if the previous mentioned risk factors are also present.

Diagnostic and Therapeutic Management

BCL-ABL kinase inhibitors have transformed the prognosis of CML; thus, many patients taking TKIs for CML will be on therapy for 10 years or longer. Therefore, it is essential for physicians to prevent and manage acute and chronic vascular complications associated with these agents. The first step in prevention and diagnosis of PAD secondary to anticancer treatment is represented by accurate cardiovascular risk stratification, searching for preexisting CVRF and cardiovascular disease [24]. So assessment of CVRF implemented by clinical visit and ankle-brachial index measurement is strongly recommended [1]. This strategy allows identifying patients at higher risk of developing vascular complication and which can thus benefit of some precautions, such as selection of the optimal second- or third-line TKI and doses. Due to the high risk of development of PAD, it should be avoided to administrate nilotinib and ponatinib as first-line therapy in patients with multiple CVRF if other agents are available [12]. Different strategies have been proposed (Table 9.2). One is to start with imatinib in most patients and to switch to second-line TKI only when a suboptimal or no response is seen or the patient is at high risk to transform to accelerated phase (AP)/blast phase (BP). Another possibility in high-risk patients (for both AP/BP risk and vascular complications risk) is to start with bosutinib or to administer bosutinib after 3 to 6 months of imatinib therapy. The possibility of inducing a stable, deep molecular response (MR) with nilotinib, dasatinib, or ponatinib may be considered as alternative and then continuing therapy with imatinib or bosutinib for another 2 years.

Table 9.2 Proposed strategies to minimize the risk of VAE evolution in patients with CML

Pretreatment:
Selection of patients and selection of TKI based on comorbidities, cardiovascular risk factors, and the biology of CML
Exclude patients with cardiovascular comorbidities from therapy with nilotinib and ponatinib
Exclude patients with cardiovascular risk factors (high ESC score, molecular risk factors) from therapy with nilotinib and ponatinib
During treatment (treatment algorithms, schedules, and dosing):
Frontline use of imatinib in patients with CP CML
Keep nilotinib and ponatinib exposure times to a minimum
Reduce the dose of nilotinib or ponatinib if possible
Avoid sequential application of nilotinib and ponatinib
Switch to other TKI with lower risk concerning VAE development once a deep MR has been reached (prophylaxis)
Switch to other TKI with lower risk concerning VAE development once a VAE has developed
Alternative treatment concepts and co-medication:
Discontinue TKI therapy after 2 years in deep MR (MR4 or deeper)
Stem cell transplantation = SCT (young and fit patients)[a]
Antibody-based CML stem cell eradication followed by TKI discontinuation
Discontinue TKI therapy and introduce immunotherapy or other experimental therapies as maintenance
Prophylactic co-medication with aspirin, gliptins, and statins
TKI rotation therapy: Combining more toxic TKI with less toxic TKI

Adapted from Valent et al. [10]
CP chronic phase, *CML* chronic myeloid leukemia, *VAE* vascular adverse event, *TKI* tyrosine-kinase inhibitor, *MR* molecular response, *ESC* European Society for Cardiology
[a]In young and fit patients who are potential candidates for SCT, it is of considerable importance to avoid any occurrence of a VAE before SCT. Therefore, in these patients, it is as important to select optimal and safe therapy as in older patients with comorbidities

However, this strategy does not prevent at all the possibility of PAD development, because usually several months are necessary before reaching a deep MR. An interesting alternative can be the rotational therapy, consisting in a combination of a potent but high-risk TKI (nilotinib or ponatinib)

with a safer agent (imatinib or bosutinib) in 1- to 3-month intervals [25, 26]. All these strategies, however, need to be tested in large clinical randomized trials.

Once PAD has occurred, management relies first on the grade of vascular disease. In case of Fontaine stages I or II, patients require risk factor control and periodic clinical, metabolic, and hemodynamic follow-up [27]. In these cases, it is possible to maintain therapy with nilotinib or ponatinib, usually at low doses. It could be suggested to start therapy with aspirin, and antidiabetic drugs or cholesterol-lowering agents, or antihypertensive drugs, could be added if metabolic disorders or hypertension develop. However, the development of high-grade PAD is a more challenging question, due to the problems related to interruption of potent BCR-ABL TKIs therapy. In some cases, it is possible to switch to TKIs with safer vascular profile (imatinib or bosutinib). In selected patients with deep and long-lasting MR (MR4 or deeper), discontinuation of TKI treatment may be an option. Moreover, revascularization should be individualized and discussed in a multidisciplinary meeting with experts in hematology, vascular surgery, and cardio-oncology [1, 28].

Stroke

Incidence and Pathophysiology

Cerebrovascular disease, such as transient ischemic attack and ischemic stroke, can complicate anticancer treatment, in particular head and neck radiotherapy (Table 9.3). The risk of stroke is, in fact, increased, at least doubled, after mediastinal, cervical, or cranial radiotherapy, with the exception of adjuvant neck radiotherapy for breast cancer where carotid exposure is minimal [29, 30]. The risk of developing cerebrovascular disease is higher when radiotherapy exposure occurs in childhood than in adulthood. Radiation vasculopathy is the precursor to ischemic stroke in patients who have been treated with head and neck radiotherapy for cancer [31, 32]. Chronic radiation vasculopathy affecting medium and large intra- and extracranial arteries is characterized by increasing rates of hemodynamically significant stenosis. The pathogenesis of radiation-induced cerebrovascular complication, however, is not totally known, and there are two main hypotheses. In particular, while some authors consider radiation occlusive vasculopathy as a form of accelerated atherosclerosis, others considered it as a distinct disease secondary to the initial radiation insult to the vasa vasorum [33–37]. Fonkalsrud et al. analyzed the evolution of radiation vasculopathy in canine femoral arteries after a net dose of 40 gray [38]. By 48 h, there was extensive endothelial damage with nuclear disruption, platelet aggregation, and fibrin deposition; the intima and media remained intact, but the adventitia already showed minor fibrosis and hemorrhage. By 1 week, no normal endothelial cells were seen, and by 3 weeks, there was destruction of the internal elastic lamina and marked thickening of the endothelium. By 6 weeks, the media was hypocellular. By 4 months, there was focal necrosis and fibrosis of the media, accompanied by chronic inflammation and minimal thrombosis of the adventitia. The medial and adventitial fibrosis narrowed the vessel lumen.

Table 9.3 Radiation-induced vasculopathy

	Vasculopathy
Cause	Radiotherapy (mediastinal, cranial, cervical)
Physiopathology	Endothelial damage, fibrosis, medial necrosis, accelerated atherosclerosis
Location	Small vessels and medium or large vessels
Evaluation	Clinical visit, ankle-brachial index, carotid duplex ultrasound
Screening	Five years after radiation exposure, then every 5 years or earlier if atherosclerosis detected
Treatment	Antiplatelet treatment; severe stenosis may require stenting or surgery

It is also known that irradiation induces an increase in oxidative stress involved in the formation of vascular damage. Some pro-inflammatory molecules (cytokines and growth factors) can stimulate radio-induced endothelial proliferation, fibroblast proliferation, collagen deposition, and

hence the fibrosis leading to the development of atheromas. Endothelial damage secondary to irradiation induces the secretion of thrombomodulins, which, together with other pro-inflammatory molecules, increase the attraction of leukocytes on the endothelium (chemotaxis), resulting in subendothelial inflammatory infiltrate. The pathophysiology of radiation-induced vasculopathy can be thus summarized in the following mechanisms occurring in medium and large vessels—vasa vasorum occlusions with medial necrosis and fibrosis, adventitial fibrosis, and accelerated atherosclerosis—leading to increased carotid stiffness and intima-media thickness and advanced atherosclerosis (occurring >10 years after radiotherapy) [39, 40]. However, while it is clear that no doses of radiotherapy can be considered safe, there are not exhaustive information if and which dose can be safer.

Even if radiotherapy is the main "iatrogenic" cause of cerebrovascular accident (CVA) in patients affected by cancer, it is not the only. There are, in fact, evidences of the role of traditional chemotherapy and new target therapy in higher incidence of stroke in neoplastic patients. Cisplatin and 5-fluorouracil (5-FU) are the main drugs involved. More than 30 years ago, Goldhirsch et al. [41] reported an acute CVA in a patient receiving a cisplatin-based treatment. Other case reports followed [42–45].

The pathophysiology is probably multifactorial. Cisplatin is responsible for a hypercoagulability state secondary to a cisplatin-induced reduction of C-reactive protein and increased von Willebrand factor and tissue factor level. Moreover, cisplatin induces endothelial dysfunction responsible for increased intima-media thickness and reduced production of nitric oxide [46] and may cause nephrotoxicity with renal magnesium wasting that lead to a vasoconstriction [45].

5-FU is an antineoplastic agent which has also been connected with increased incidence of ischemic strokes, and cases are also reported following combined treatment with both 5-FU and cisplatin [44, 47]. It was demonstrated that 5-FU causes direct endothelium-independent vasoconstriction of vascular smooth muscle in vitro [44]. However, ischemic stroke has to be differentiated from leukoencephalopathy with stroke-like presentation which is a rare complication of chemotherapeutic agents, among which is 5-FU, and is characterized by specific finding on cerebral magnetic resonance [48–50].

Finally, even if cases of CVA after treatment with bevacizumab were reported [51], the meta-analysis conducted by Ranpura et al. concluded for a no significant risk of stroke in patients treated with bevacizumab respect to controls [52]. However, probably a higher risk of cerebral ischemic events has to be expected due to endothelial injury secondary to inhibition of VEGF signaling and subsequent risk of arterial thrombosis, typical of this group of drugs [53, 54]. Anthracyclines, more commonly associated with cardiac toxicity, may also increase the risk of stroke through several pathophysiological mechanisms involving carotid arteries such as oxidative stress, vascular inflammation, and apoptosis. Indeed, anthracyclines can induce both an acute and chronic carotid damage, the first related to endothelial dysfunction and increase of smooth muscle tone and the second to accelerated atherosclerosis and increased collagen synthesis.

More than 15 years ago, experimental models demonstrated that the exposure of animal arteries to doxorubicin for 1 to 10 weeks is able to lead apoptosis of smooth muscle cells and increased medial and adventitial thickness, and these data were confirmed later [55]. These reparative processes secondary to the chemical stress lead to structural changes within the vessel wall and extracellular matrix with increased collagen deposition and vessel wall calcification, ultimately resulting in reduced arterial compliance and increased stiffness. More recently, it has been detected through magnetic resonance imaging (MRI), in individuals receiving anthracyclines for breast cancer, an early (≈3 months) and abrupt increase of arterial stiffness, and, interestingly, this effect was dose-, age-, and CVRF-independent. Moreover, the increase of arterial stiffness can be persistent at 12 months after therapy [56–58]. Also, patients survived for ≥5 years after diagnosis of leukemia, lymphomas, and central nervous system tumors, and sarcomas treated with standard chemotherapy show

lower carotid distensibility and compliance, indicating increased arterial stiffness, when compared to controls [59].

All these results demonstrate thus that early in life, cancer survivors previously treated with anthracyclines have arterial changes indicating increased risk for premature atherosclerosis and stroke.

Diagnostic and Therapeutic Management

Patients treated with head and/or neck radiotherapy should undergo cerebrovascular ultrasound, especially beyond 5 years after irradiation, and then follow-up should be performed at least every 5 years or earlier if atherosclerosis is detected [1]. Of note, carotid lesions secondary to radiotherapy are often more extensive and commonly involve longer segments of the carotid arteries (Fig. 9.1). CT angiography is also routinely used to evaluate carotid, subclavian, and aortic diseases related to radiation therapy [60]. To date, no randomized trial has assessed the medical treatment option for primary or secondary stroke prevention in this patients' group. A strict control of traditional CVRF should be strongly recommended, and antiplatelet treatment may be considered. Significant carotid stenosis may be treated by surgery or stenting [28, 61–64]. Even if neither approach appears to be clearly superior, different studies showed a higher incidence of restenosis after carotid angioplasty and stenting of radiation-induced vascular stenosis, compared to surgical results [65–67].

The relationship linking increased arterial stiffness with atherosclerosis and risk of stroke is

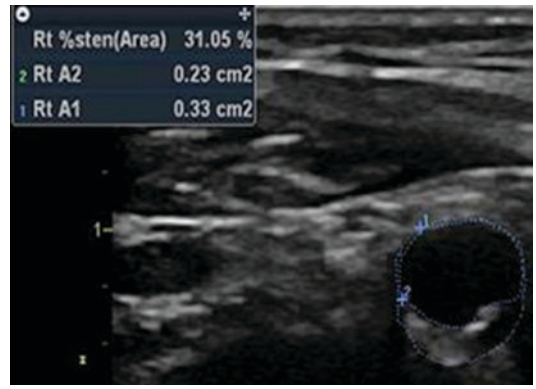
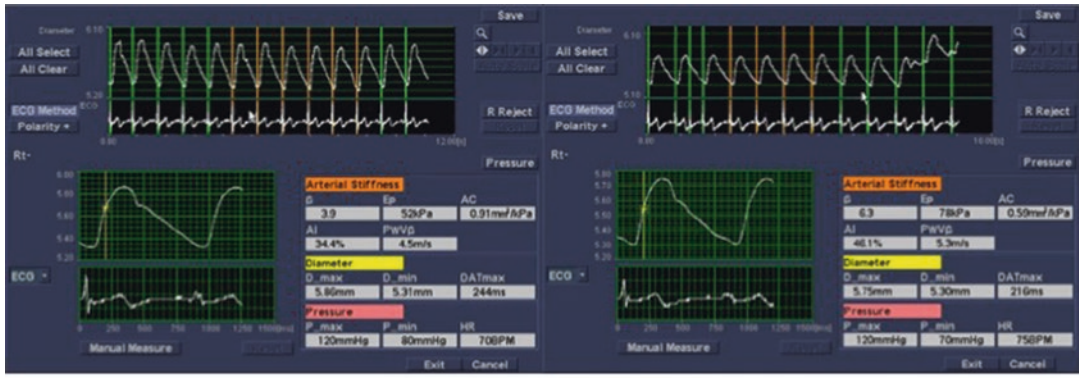


Fig. 9.1 Carotid ultrasound image showing atherosclerotic plaque in a patient without CVRF underwent neck radiotherapy



A. Baseline	B. 3 months after antracyclines
Beta index 3.9	Beta index 6.3
PWV 4.5 m/sec	PWV 5.3 m/sec
BP 120/80 mmHg	BP 120/70 mmHg
HR 70	HR 75

Fig. 9.2 Measurement of beta-index and PWV through echotracking at baseline and 3 months after starting chemotherapy with anthracyclines, showing early increased arterial stiffness

Table 9.4 Unsolved problem for including arterial stiffness assessment within the stroke risk management in cancer patients

Small studies, small patients
Age, race, and gender effects
Reversibility
Cancer-related effect on vessels
No drug-specific studies (often combined therapy)
Radiotherapy additional effects
Comorbidities
Unknown relationship with outcome
Short follow-up studies

well recognized. Accordingly, it is reasonable to advocate that efforts should be directed at monitoring increased arterial stiffness and managing CVRF in cancer patients treated with drugs which may potentially impair vascular elasticity (i.e., anthracyclines and anti-VEGFR). Applanation tonometry and/or echotracking are two main available modalities in clinical practice for this purpose (Fig. 9.2) [68]. Moreover, being PWV an independent predictor of cardiovascular morbidity and stroke, we can better stratify patients' prognosis. Nonetheless, larger prospective studies are needed to determine the predictive value of PWV in this population and its utility as a screening modality. Unsolved problems on this issue are detailed in the Table 9.4.

In patients at risk of ischemic stroke, undergoing treatment with platinum compounds is important to stabilize CVRF in order to prevent vascular ischemia. Carboplatin, second-generation platinum, shows an improved toxicity profile. Additional agents, e.g., vitamins, selenium, resveratrol, and melatonin, reduce endothelial cell oxidative stress and inhibit inflammation, thus exerting beneficial effects by suppressing cisplatin-related oxidative injury [45].

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Valvular Heart Disease

10

Ines Paola Monte and Gyanendra Kumar Sharma

Etiology

Valvular heart diseases (VHD) may be observed in patients with cancer for several reasons, including preexisting valve lesions, radiotherapy, infective endocarditis, and secondary to left ventricle (LV) dysfunction. Over the years, the incidence of cardiovascular events has increased in these patients, especially in younger survivors who do not have traditional risk factors and are treated with thoracic radiotherapy for certain malignancies, such as Hodgkin's lymphoma and breast cancer. It has been known since the 1960s that valve dysfunction can be caused by cancer therapy, both with radiation and more recently chemotherapy. Due to the latency of the valve dysfunction presentation, the diagnosis is late and more often incidental, and most of the studies exploring the effects of radiation and chemotherapy on heart valves have been retrospective and observational.

Radiotherapy, as adjuvant to chemotherapy or as monotherapy, has contributed to decrease the mortality rate from certain cancers over the past 60 years. In patients with Hodgkin's lymphoma, radiation has been used since 1940 and when combined with chemotherapy improved survival by nearly 60% [1].

In patients with breast cancer, recurrence rates have decreased by nearly half and resulting in a 60% 15-year survival [2]. Radiotherapy is also beneficial for other cancers adjacent to the heart, such as metastatic testicular, lung, or esophageal. Therefore, the involved field of radiation often covers portions of the heart and likely to induce cardiac damage.

Radiation-induced VHD is an increasingly recognizable entity occurring late after mediastinal radiotherapy, affecting 10% of treated patients, with a median time to diagnosis of 22 years, while a minority of patients have a complete normal function of aortic valves at the 20-year follow-up [3, 4].

In patients with Hodgkin's lymphoma, the dose of the heart valve radiation can increase the risk of clinically significant VHD as the first cardiovascular event after treatment. This has recently been shown in a cohort of 1852 survivors of lymphoma in the Netherlands. Thirty-year cumulative risk of valvular heart disease stratified by radiation received was 3%, 6%, 9%, and 12% for total radiation <30Gy, 31–35Gy, 36–40Gy, and >40Gy, respectively. The risk increases by dose in a greater than linear pattern between 30 and 40Gy. While for patients with mediastinal involvement currently treated with

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20 or 30Gy, the absolute difference in 30-year VHD risk in irradiated vs non-irradiated patients was estimated to be 1.4% [5].

The natural history of VHD varies with radiation dose, by extension, and the decade in which the patient was treated. A study of survivors irradiated with obsolete protocols between 1965 and 1995 revealed 13- and 30-year cumulative incidences of 10% and 20%, respectively. Prior history of radiation increased the risk of VHD for these patients sevenfold [6].

The mechanism of radiation-induced damage to heart valves is not clear. Cardiac damage includes diffuse fibro-calcific thickening of the valve without derangement to the underlying structure and signs of chronic inflammation such as neovascularization or thrombus formation. The earliest change appears to be the formation of valvular retractions and accompanying regurgitation preferentially involving the mitral and aortic valves, occurring within the first 10 years. The process causes fibrosis and calcification of the aortic root, aortic valve cusps, mitral valve annulus, and the base and mid-portions of the mitral valve leaflets, sparing the mitral valve tips and commissures, thickening the mitral-aortic curtain (fibrous tissue between the aortic and mitral valves) [7–11].

Nadlonek demonstrated that irradiation of aortic interstitial cells induces an osteogenic phenotype [12]. This resulted in increased formation of osteogenic factors, including bone morphogenetic protein 2, osteopontin, alkaline phosphatase, and the transcription factor Runx2, all critical factors for bone formation and calcification of valves exposed to radiation.

The progression to fibrotic thickening and calcification of the valves occurs much later, with stenosis often appearing 20 years after radiation. Observational studies demonstrated a long latent interval between radiation exposure and development of valve dysfunction. Although not linear, there is a progressive increase in development of valve dysfunction over time. VHD also manifests after decades following exposure to radiation with a preponderance to involve left-sided valves and a major prevalence of subclinical valve thickening before valve dysfunction [13–18]. Despite being anterior, pulmonary valve is rarely affected. It appears that high pressure on the left side makes valves more vulnerable to adverse consequences of radiation.

Radiation dose, interval from irradiation, and the use of sequential chemotherapy are linked to development of radiation-induced valve disease. The combined risk of radiation and chemotherapy for the development of valvular heart disease is greater and increases for the older patients, regardless of follow-up duration. The valvular dysfunction in the anthracycline-treated patients is more often due to aortic valve degeneration than mitral valve; probably anthracyclines could have a direct toxic effect on valves, not simply functional regurgitation related to cardiomyopathy and ventricular dilation [19].

The synergistic role of chemotherapy and radiation has been described in LV functional impairment from anthracyclines, such as doxorubicin. It can produce systolic and diastolic dysfunction via toxic effects on the myocardium. Boekel showed a slightly increased risk associated with left- vs. right-sided radiation (HR 1.19; 95% CI 1.04–1.36) [20].

Several studies in patients with Hodgkin's lymphoma showed that if >63% of the left atrium received 25Gy or if >25% of the left ventricle received 30Gy, this predicted development of aortic or mitral valve disease, and the risk of valve defects increases as the percentage volume of heart chambers receiving 30Gy [20]. The overall incidence of valvular dysfunction is lower for population with breast cancer (0.5% with left-sided breast cancer and 0.35% on the right) compared to Hodgkin's lymphoma [21]. In patients with breast cancer, the dose of radiation to the heart may be two times or more with left side radiation as compared to the right side (Table 10.1) [22].

Diagnosis

Radiation-induced VHD is commonly diagnosed after a long latent period, in the context of clinical symptoms of heart failure that valve insufficiency is either contributing, or suspected VHD on the basis of a new murmur.

Table 10.1 Risk factors for radiotherapy-induced VHD

Increase dosage of radiation	The risk of developing VHD increases as radiation dose increased with a linear pattern between 30 and 40Gy
Interval from irradiation	Progressive increase in development of VHD over time
Left-sided breast cancer	Radiation of the heart area
Combination with anthracycline-based chemotherapy	Anthracycline-containing chemotherapy increases the risk of VHD in patients receiving mediastinal radiotherapy
Decade in which the patient was treated	Effects of obsolete protocols used between 1965 and 1995

The evaluation includes identification of anatomical valve abnormalities and valve dysfunction and assessment of the functional consequences of valve dysfunction on the ventricles. Echocardiography is the optimal imaging technique for diagnostic and therapeutic management.

Baseline and repeated transthoracic echocardiography after radiotherapy involving the heart are recommended in patients with cancer for the diagnosis and follow-up of VHD. Transesophageal echocardiography adds important information, especially when significant calcification or fibrosis is present and limits transthoracic image quality. In addition, 3D echocardiography may be helpful in the evaluation of mitral valve morphology. CMR may also be useful in those with suboptimal echocardiography, or results are incomplete or discrepant and can provide assessment of myocardial fibrosis. CMR and CT may be used to assess the severity of VHD, but cardiac CT is mainly useful for detecting extensive calcifications of the ascending aorta, which may lead to a higher operative risk and sometimes prohibit conventional cardiovascular surgery [23].

The criteria for diagnosis do not differ from that used for traditional degenerative valvular pathology, and early echocardiographic findings are characteristic but nonspecific. Diffuse thickening of valve leaflets and subvalvular apparatus may occur without functional abnormality, but there are several unique characteristics of radiation-induced damage (Table 10.2).

Table 10.2 Echocardiographic characteristics of radiation-induced VHD

Uniform valvular thickening from fibrosis
Left-sided valves > right-sided valves; particularly aortic valve
Mitral-aortic curtain thickening
Regurgitation prior to stenosis
Preservation of mitral commissural fissures

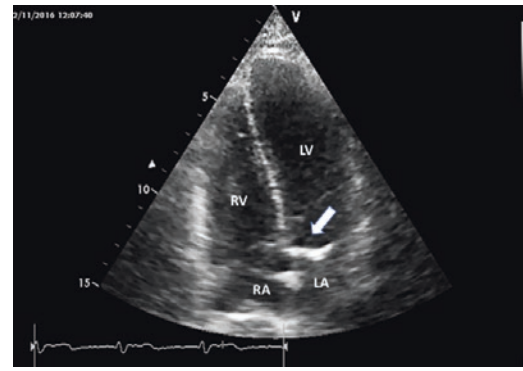

Fig. 10.1 Calcifications of mitral-aortic curtain (arrow). Four chambers view: RV right ventricle, LV left ventricle, RA right atrium, LA left atrium

Left-sided valves are affected preferentially over right-sided valves, particularly aortic valve. Moderate or severe aortic, mitral, tricuspid, and pulmonary regurgitation are shown in 15%, 4.1%, 4.1%, and 0% of patients, respectively, and aortic stenosis in 16% of patients who were irradiated >20 years previously compared with <0.5% of age-matched and sex-matched controls [24].

Typically, the valves become thickened and restricted as collagen is deposited and ultimately calcified. The restriction leads first to regurgitation and then can progress to stenosis if severe. Focal calcification of the valve leaflet/cusps involves the mitral-aortic curtain Brand—anterior leaflet of the mitral valve extending to the aortic root (Figs. 10.1 and 10.2)—classically affected with gradual thickening extending all the way from the mitral valve to the aortic root and can be seen easily on parasternal windows [25].

Radiation-induced VHD can often present with diffuse thickening similar to rheumatic mitral disease, but unlike rheumatic valve disease, there is a lack of commissural fusion. The two can be distinguished on 3D echocardiography by

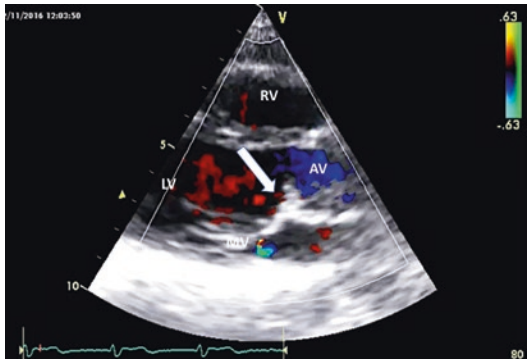

Fig. 10.2 Calcifications of mitral-aortic curtain (arrow). Long axis view: RV right ventricle, LV left ventricle, AV aortic valve, MV mitral valve

the loss of the commissural fissure that is characteristic of rheumatic disease but not seen with radiation VHD [26].

Most valvular dysfunction is mild-moderate and only requires surveillance, but it is a progressive disease and can occasionally become severe requiring interventional evaluation.

Management

The European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) recommend a focused yearly history and physical examination with echocardiography in symptomatic patients. For asymptomatic patients, the EACVI/ASE consensus document recommends a screening transthoracic echocardiogram at 10 years postradiation and serial exams every 5 years thereafter in patients with normal valves [23].

An algorithm proposed for follow-up of patients exposed to mediastinal radiotherapy suggests follow-up 2–3 years in patients with structurally abnormal valves, such as calcification or thickening, but minimal valve dysfunction. Patients with moderate valve disease require yearly follow-up. Patients with severe valve dysfunction should be assessed for valve surgery taking into consideration high-risk features and sequelae of radiotherapy, such as pericardial constriction, left ventricular impairment, and pulmonary fibrosis (Fig. 10.3) [24].

There are no specific guidelines for the timing of surgery in patients with radiation-induced valve disease, and therefore, this should be performed according to current international guidelines for VHD.

Aortic valve replacement is the most common procedure in these patients, though mitral and tricuspid valve disease may also require intervention. Cardiac surgery is also frequently challenging in such patients because of mediastinal fibrosis, impaired wound healing, and associated coronary artery, myocardial, and pericardial disease. Therefore, patients should be referred to a center with more experience in operating on these patients.

Crestanello reported that 32% of previously irradiated patients who underwent mitral and/or tricuspid valve repair experienced severe valve deterioration, likely because of progression of radiation-induced tissue injury. In light of these findings and the known dangers of reoperation in this cohort, the authors concluded that mitral and tricuspid valve replacement may be superior to repair in these patients [27].

Over the past several years, transcatheter aortic valve implantation (TAVI) has proven equal or superior to surgical valve replacement in high-risk patients. In the PARTNER Registry, approximately 5% of patients enrolled had a history of prior chest wall radiation, with initial favorable results [28].

Recently guidelines on VHD management suggest that in patients who are at increased surgical risk (STS or EuroSCORE II >4% or logistic EuroSCORE I >10% or other risk factors such as frailty, porcelain aorta, or sequelae of chest radiation), the decision between surgical aortic valve replacement and TAVI should be made by the heart team according to the individual patient characteristics [29].

Radiotherapy techniques have evolved over the past few decades. Techniques to reduce radiation dose to normal tissues and/or the radiotherapy field size have emerged. New techniques, including intensity-modulated radiotherapy and proton therapy, are better able to spare normal tissue by improving conformity to target structures. The optimal field size and technique and

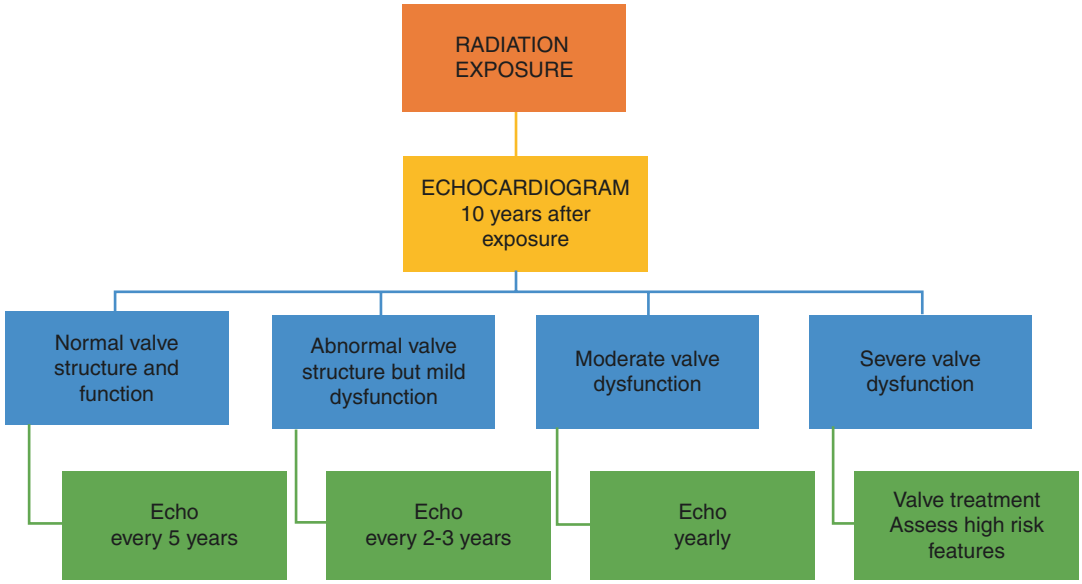

Fig. 10.3 Algorithm for follow-up of patients exposed to mediastinal radiotherapy

respiratory gating depend on the individual patient characteristics, including tumor size, location, and nodal involvement, and the use of individualized therapy could minimize normal tissue toxicity and long-term complications [30].

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Arterial Hypertension

11

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Introduction

Approximately one out of three persons in the world is affected by hypertension. Representing the most common reversible risk factor for cardiovascular and cerebrovascular diseases, it contributes dramatically to mortality and morbidity worldwide.

The prevalence of hypertension in cancer patients is similar to that of general population, so that it is the most common comorbidity even in this setting.

The issue of hypertension in patients being treated for cancer is paramount because of two main findings: firstly, the concern that a preexisting hypertensive status may increase the risk for the development of cardiac adverse effects, including left ventricular dysfunction, after specific antineoplastic treatments, i.e., anthracyclines. Secondly, new-onset hypertension has emerged as an adverse event for several cancer therapies, in particular for the newer anti-vascular endothelial growth factor agents. These considerations stress the importance of a cardiological evaluation prior, during, and after cancer treatments.

After briefly reviewing the general concepts about arterial hypertension, this chapter will focus on the main implications of hypertension in the oncologic patient, especially if treated with cardiotoxic agents, on hypertension due to antineoplastic treatments, and, finally, on the comprehensive management of this condition in the cancer patient.

General Concepts on Hypertension

There is a linear relationship between blood pressure (BP) values and cardiovascular (CV) events. Affecting one billion people worldwide, hypertension is the leading risk factor for stroke and heart failure. Overall, it is the predominantly modifiable risk factor for CV deaths, with more than half of deaths from coronary artery disease or stroke occurring in individuals with hypertension. Hypertension and diabetes mellitus (DM) represent, furthermore, the main causes of end-stage renal disease [1].

When approaching hypertension, it should be kept in mind to consider not the disease *alone* but the whole spectrum of CV risk. This consideration has emerged over years from the finding that concurring risk factors in the same individual may potentiate each other. Current European Society of Cardiology (ESC) guidelines propose a stratification of risk in very high, high, moderate, and low, basing on age, gender, smoking status, BP,

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and total cholesterol values through a validated system named SCORE, which predicts 10-year risk of a first fatal atherosclerotic event. Individuals with known previous CV disease(s) or DM with organ damage or severe chronic kidney disease automatically belong to the very-high-risk category [1, 2]. A similar tool (atherosclerotic CV disease risk estimator) was developed by the American Heart Association (AHA), with high risk defined as >10% risk of events at 10 years or as having concurrent diabetes mellitus or chronic kidney disease [3]. Management strategies should be calibrated depending on CV risk category, meaning that a more aggressive approach on every single risk factor should be considered for those at higher risk.

Hypertension, according to ESC guidelines, is defined as either systolic BP (SBP) values ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg, whereas optimal BP values are considered <120/80 mmHg. Recently published AHA guidelines define instead hypertension if BP values are ≥130/80 mmHg. The degree of hypertension may be divided in different grades, as shown in Table 11.1. These cutoff values refer to the so-called *office* BP, which means BP measured in a medical setting. BP measurements obtained other else represent the *out-of-office* BP. This distinction may have important implications. The rationale and importance of out-of-office BP are that it provides a more true assessment of actual BP, avoiding, for example, the phenomenon of *white-coat* hypertension (hypertension induced in the medical environment) and offering a representation of BP average values at different times of the day. The cutoff values for out-of-office hypertension are therefore different from those used for office BP measurement, and are shown in Table 11.2, according to the ESC guidelines. Out-of-office BP is additionally subdivided in ambulatory BP monitoring (Holter BP monitoring) and home BP monitoring. While elevated office BP values and normal out-of-office values are defined as white-coat hypertension, the opposite situation (normal office BP values with elevated out-of-office values) is defined as *masked* hypertension. Out-of-office monitoring is particularly indicated when suspecting one of these two conditions.

Table 11.1 Blood pressure degrees according to different contemporary guidelines

	SBP (mmHg)	DBP (mmHg)
European Society of Cardiology guidelines		
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110
American Heart Association guidelines		
Normal	<120	<80
Elevated	120–129	<80
Stage 1 hypertension	130–139	80–89
Stage 2 hypertension	≥140	≥90

DBP diastolic blood pressure, *SBP* systolic blood pressure

Table 11.2 Cutoff values for hypertension by office and out-of-office measurements, according to ESC guidelines

	SBP (mmHg)	DBP (mmHg)
Office BP	≥140	≥90
Ambulatory BP, daytime	≥135	≥85
Ambulatory BP, nighttime	≥120	≥70
Ambulatory BP, 24 h	≥130	≥80
Home BP	≥135	≥85

BP blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

Hypertension is divided in secondary hypertension and essential or primary. Overall, essential hypertension represents the vast majority of all hypertensive patients. Suspicion for a secondary form of hypertension should be considered based on patient's history and examination, in particular in case of severely high BP values especially in the younger patients, worsening hypertension, presence of organ damage disproportionate to the duration of hypertension, and poor or absent response to therapy. When suspected, secondary hypertension must always be investigated, being a potentially reversible condition.

All these considerations conflict with the great difficulty in managing hypertension. Surely, the asymptomatic condition of the disease causes a significant delay in diagnosis. Latest estimates show that while around two-thirds of hypertensive patients are aware of their condition and

undergo a specific treatment, BP is controlled only in a percentage that varies between 30% and 50%. Moreover, it is to consider that even in those whose BP values are under control, just one-third is protected from subsequent CV events, because of many interactions, for example, a long-standing disease prior to initiation of medical treatment.

As for the definition of hypertension, there is no consensus between guidelines for target values of BP. The 2013 ESC guidelines outline how there is no clear evidence of a benefit from lowering SBP less than 140 mmHg, even in high-risk patients. As well, DBP goal is <90 mmHg, except for diabetic patients, whose target value is 80–85 mmHg. In elderly patients a goal of SBP < 150 mmHg is currently accepted. However, some clinical trials highlighted that lower BP values may result in lesser CV events: the SPRINT trial, published in 2015, showed that an intensive SBP lowering of <120 mmHg in high-risk patients resulted in lower rates of major CV events and death from any cause. Notably, diabetic patients were not included in the trial. According to the 2017 AHA guidelines, patients at high CV risk should be treated when BP values are ≥130/80 mmHg, and the goal should be of keeping BP under this cutoff. Otherwise, antihypertensive treatment should be started when BP values are ≥140/90 mmHg.

Lifestyle changes, undoubtedly substantial part of both prevention and treatment of hypertension, are paramount because they contribute to reduce CV risk at a greater extent.

Many pharmacologic agents exist for the treatment of hypertension. The general consensus is that there is no superiority of one class of agents over any of the others: the choice of the treatment may rather depend on concurring conditions. The major classes of antihypertensive drugs are diuretics, beta-blockers, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs)—all are suitable as agents for the initiation of treatment. Starting with a combination therapy is generally preferred, if not in all patients, at least in those with higher BP values or with high or very high CV risk. Given this, drugs to be preferred are of course those more prone to association therapy (notably, the only association not recommended is that between ACEi and ARBs). Trials and meta-analysis have indeed shown that combining two drugs (from any classes) results in a greater reduction in BP values than increasing the dose of a single agent. The timing of a first intervention, with drugs rather than with lifestyle changes alone, depends on the CV risk, degree of hypertension, and the presence of target organ damage. It is generally recommended, irrespectively of the type of starting approach, to close monitor patient's response to decide whether to implement therapy. For example, AHA guidelines suggest a follow-up evaluation after 3–6 months in patients at low CV risk, for whom a lifestyle approach is decided, and a follow-up after 1 month in those at higher risk starting straight with medications.

Hypertension as a Risk Factor for Cancer

Hypertension as a preexisting condition has been widely investigated in neoplastic patients. The association between hypertension and development of cancer was object of many studies. The very first analysis suggesting hypertension to cause an increased risk of cancer dates back to 1975 [4]. Since then, several others were conducted, but results have been conflicting.

In a large Finnish cohort of more than 20,000 patients followed for a mean of 16 years, there was no difference in the incidence of any cancer between hypertensive and normotensive subjects, though a relation for some type of cancer was observed [5]. Similar results were reported by a Swedish study on 6614 elderly patients (mean age 76 years old, mean follow-up 5 years). This latter study also confirmed findings about the absence of a speculated relation between antihypertensive drugs and the development of cancer [6]. Another subsequent meta-analysis comprising more than 300,000 patients from 70 trials ruled out a possible link, not recording any association between cancer incidence nor mortality

with any class of antihypertensive drugs [7]. In contrast to these data, the largest analysis to date (577,799 participants, average follow-up 12 years) reported a modest but significant association between hypertension and cancer incidence in men and between hypertension and cancer mortality in men and women [8]. Other studies also found an increased rate of cancer mortality in hypertensive patients [9].

To note, it cannot be excluded that these findings are in some part biased due to a greater attention given to hypertensive patients (the more frequent medical evaluations, the higher probability of being diagnosed from other diseases), but also to a lower CV mortality thanks to medication, which allows developing of cancer with aging.

As previously reported, while evidence of an association between hypertension and any type of cancer is still not defined, it does exist a correlation with specific cancer subgroups.

The most frequently addressed is kidney cancer, and hypertension was found to significantly increase its risk in several analyses, though degree and characteristics of this association are not uniform in all studies. A large US data support the association for both men and women independently from obesity and smoking [10]. In a Taiwanese cohort, hypertension significantly increased the risk of kidney cancer only in women and was also related with endometrial cancer in women <50 years old [11]. Higher incidence of endometrial cancer in hypertensive women was found in the Finnish analysis as well [5]. In other cancer types, as for prostate cancer and those from the gastrointestinal tract, hypertension contributes to the risk of cancer as part of the metabolic syndrome [8, 12]. An increased risk of breast cancer was reported in postmenopausal hypertensive women [13].

Hypertension as a Predisposing Factor for Cardiotoxicity Due to Anticancer Drugs

Another concern with hypertensive patients comes from findings that not only higher cancer mortality was reported but also more frequent adverse events related to specific antineoplastic treatments. It is the case of anthracyclines. Cardiotoxicity induced by this class of drugs is well known and is dose-dependent, and its peculiarity is that it may occur even years after the anthracycline-based treatment has ended. A convincing reason for this characteristic timing is proposed in the "multiple-stress" or "multiple-hit" hypothesis. Briefly, anthracyclines' damage on cardiomyocytes and cardiac stem cells, driven by production of reactive oxygen species, represents the substrate for subsequent insults on the heart, which results weakened and unable to adapt or self-heal. Basically, these latter insults may be merely represented by aging. In this context, a previous CV disease, and specifically hypertension, makes the heart more susceptible to develop the well-known anthracyclines-induced left ventricular dysfunction [14, 15]. In a cohort of women aged 66–70 years old, hypertension, along with diabetes and coronary artery disease, was found to be a strong predictor of heart failure due to anthracycline adjuvant treatment [16]. Among patients with diffuse large B-cell lymphoma older than 65 years, hypertension was the strongest predictor of heart failure due to doxorubicin [17]. In another analysis of patients affected by non-Hodgkin's lymphoma treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), those with preexisting hypertension were significantly more likely to develop subsequent heart failure than those normotensives [18]. Moreover, the study showed how hypertensive patients were more prone to undergo a discontinuation of the antineoplastic therapy or a delay in treatment or a reduction in anthracycline doses, implying that hypertension may also render less effective chemotherapy.

Practical approaches to avoid or at least better manage anthracyclines toxicity have been proposed [14, 19]. High-risk patients must be identified prior to the beginning of anthracycline treatment. For these subjects cardioprotective strategies are advised and should be taken into consideration. These mainly consist of using dexrazoxane, choosing a liposomal anthracycline, and/or starting cardioactive drugs in pri-

mary prevention (even if there are no definite and unequivocal data in regard of this latter option).

Given that hypertension increases the risk of anthracycline cardiotoxicity, the goal is to have on-target BP values, meaning it may be needed to implement therapy in those already taking drugs but not on target or start a new therapy for those not undergoing a specific treatment. In the oncologic patients taking anthracyclines, those drugs with an effect both on hypertension and on preventing heart failure are recommended, namely, second-generation beta-blockers and ACEi or ARBs. In those patients already on treatment, it may be reasonable even to switch from other antihypertensive medicaments to these classes of drugs. Moreover, there is evidence for some of these specific molecules to directly protect against effects of anthracyclines. Carvedilol has shown to reduce mitochondrial dysfunction [20] and the production of reactive oxygen species and of proapoptotic mRNA expression [21]. It is therefore recommended as beta-blocker of choice in anthracycline-induced heart failure. Furthermore, in a small cohort of 25 patients planned to be treated with adryamicin or epirubicin, the preventive administration of carvedilol resulted in less systolic and diastolic cardiac dysfunction, compared to matched controls, at 6 months follow-up [19]. Similar results were reported for nebivolol [22], telmisartan [23], and valsartan [24]. In those patients already in therapy with a beta-blocker and/or an ACEi or an ARB, it may be considered to switch their medication to one of these molecules. Data from retrospective analysis also enhance a possible advantage from statin therapy [25].

Often used in combination with anthracyclines, trastuzumab is an inhibitor of the human epidermal growth factor receptor 2 (HER2). Its cardiotoxicity is low when administered without anthracyclines and has substantial differences. Left ventricular dysfunction induced by trastuzumab is dose-independent, manifests during chemotherapy, and is usually reversible. At the basis of its mechanism, it is not, indeed, cell death but transient mitochondrial and myocardial contractile protein dysfunction. Rate of heart failure occurrence due to trastuzumab therapy alone is reported to be lower than 4%. Patients at higher risk of trastuzumab-induced heart failure are those already previously exposed to anthracyclines and those with a preexisting CV condition, in particular left ventricular systolic dysfunction and hypertension [26, 27].

Hypertension Caused by Antineoplastic Treatments

More than one-third of cancer patients develops hypertension in the natural course of their disease.

Elevation of BP is related to age, cancer type, and cancer therapy. However, it may be seen in all cancer patients. A retrospective analysis of more than 25,000 cancer patients found an incidence rate of new-onset hypertension of more than 32 cases per 100 person/year. Hypertension presented across all cancer types, though its severity varied consistently for each sort of neoplasm. Moderate hypertension was seen more frequently in renal and lung cancers, and severe hypertension in gastric, ovarian, prostate, and lung cancers, while hypertensive crisis was more common in gastric, ovarian, lung, and colorectal cancers. Overall, the incidence of hypertension was higher during chemotherapy, even if this result may be biased by the fact that BP measurements occurred more frequently during therapy. An interesting finding, anyway, was that this relation was reported for all chemotherapy types and lines [28]. Indeed, even if specific antineoplastic treatments are more frequently associated with new-onset hypertension, it may represent a side effect of many chemotherapeutic regimens.

Moreover, hypertension may be caused also by adjuvant cancer treatments, for example, corticosteroids and erythropoietin (EPO) [29]. Corticosteroids are frequently used in antineoplastic regimens, in particular in hematologic cancers. Corticosteroid-induced hypertension mostly depends on their mineralocorticoid effects and is often easy to manage just by dietary means (i.e., intake of fluids and salt). Recombinant forms of EPO are instead used as replacement therapy in advanced kidney disease and in kidney

cancer as well. Up to 35% of patients treated with EPO develops hypertension. The pathophysiologic mechanisms proposed to cause hypertension are a direct vasopressor effect of EPO and an increase in peripheral vascular resistance due to remodeling of the vascular wall. Augmented blood viscosity may also play a role. EPO-induced hypertension treatment relies on usual drugs, though CCB may represent a good choice considering the underlying renal disease that may contraindicate ACEi and ARBs.

Data about alkylating agents come primarily from registries of testicular cancer survivors. Cisplatinum represents the basis of chemotherapeutic regimens for this cancer type. It has been observed that testicular cancer survivors are more prone to develop hypertension and metabolic syndrome. Individuals who were treated with chemotherapy (alone or in combination with radiotherapy) more frequently presented this adverse effect. The higher the cumulative dose of cisplatinum, the higher the probability for hypertension to be developed. Two Norwegian studies reported a cutoff value of 850 mg of cisplatinum, over which the association with hypertension and metabolic syndrome was more pronounced. The peculiarity for this side effect of cisplatinum is that it presents many years after the end of cancer treatments; indeed in the Norwegian cohorts, mean follow-up was of 11 years [30, 31]. Thus, hypertension due to cisplatinum is not an immediate adverse effect, and its timing strengthens the importance of a continuous follow-up of these patients, finalized to CV prevention.

Among the antineoplastic treatments, anti-vascular endothelial growth factor (VEGF) agents are those most commonly associated with new-onset hypertension or worsening of a preexisting hypertension, leading to reported incidence of hypertension-related adverse effects in up to 60% of treated patients (Table 11.3) [32]. There actually exist two groups of these drugs, humanized monoclonal antibodies that directly bind to VEGF, such as bevacizumab, and the so-called small molecules, tyrosine kinase inhibitors, such as sorafenib and sunitinib. These latter agents act on the intracellular domain of VEGF receptor (VEGFR)-2 but are not totally specific and may bind also other tyrosine kinase receptors. This molecular difference led to an initial belief that the development of hypertension was more frequent with tyrosine kinase inhibitors. On the contrary, a large meta-analysis of 77 studies highlighted a similar incidence of hypertension for both groups of drugs [33]. Overall, throughout the two groups, hypertension was the most common side effect, with a number needed to harm of six.

Table 11.3 Anti-VEGF agents and related incidence of arterial hypertension

Anti-VEGF agent	Therapeutic target	Incidence of arterial hypertension (%)
Bevacizumab	VEGF ligand	22–24
Sunitinib	VEGFR, PDGFR, KIT, FLT3, CSR, RET	15–34
Sorafenib	VEGFR, PDGFR, KIT, FLT3, RET	17–29
Axitinib	VEGFR	40
Pazopanib	VEGFR, PDGFR, FGFR, KIT, Itk, Lck, c-FMS	36–46
Dasatinib	SRC, BCR-ABL	<10
Ponatinib	VEGFR, PDGFR, FGFR, EPH, BCR-ABL, KIT, FLT3, RET, Src, TIE2	67
Regorafenib	VEGFR, PDGFR, FGFR, KIT, RET, BRAF	28–48
Cabozantinib	VEGFR, KIT, FLT3, RET, MET, TRKB, AXL, TIE2	32–37
Vandetanib	VEGFR, EGFR, RET	24

Adapted from Brinda et al. [32]

VEGF exerts its functions through three receptors, VEGFR-2 being considered the most important. This receptor promotes promitotic pathways (angiogenesis) and vascular permeability; also, it activates the endothelial nitric oxide (NO) synthase enzyme, which leads to production of NO and thus vasodilation.

Reduction in NO production due to inhibition of VEGFR-2 determines vasoconstriction and augmented peripheral resistances, hence hyper-

tension. NO is also involved in renal sodium homeostasis, and an impaired production of NO may also cause sodium retention. Anyway, contradictory results regarding the NO role in anti-VEGF agent-induced hypertension have been reported. Indeed, while on one hand decreased serum levels of NO metabolites were found with VEGF inhibition, in vitro NO bioavailability was preserved. Unconclusive data emerged also from animal models. These considerations suggested that other mechanisms beyond reduction in NO are likely involved [15, 34–37].

Firstly, VEGFR are also expressed in the kidney, specifically in podocytes. Inhibition of VEGFR results in glomerular lesion at electron microscopy and in proteinuria in up to 60% of patients affected by renal carcinoma and treated with bevacizumab. Though proteinuria is largely asymptomatic, and not clinically relevant, it has been observed that patients who develop proteinuria more frequently develop hypertension too and that proteinuria was associated with more severe grade of new-onset hypertension. Notably, despite proteinuria and new-onset hypertension, treatment with anti-VEGF agents does not cause an impairment in renal function, expressed as glomerular filtration rate [38]. Secondly, anti-VEGF agents increase levels of endothelin 1, a molecule with vasoconstrictive effect. It is not clear how anti-VEGF agents directly induced this augmented secretion, but endothelial dysfunction by itself, secondary to NO reduction, may be the cause. Moreover, the inhibition of VEGF induces endothelial cell apoptosis, resulting in a phenomenon called microcapillary rarefactions. This causes loss of small vessels and augmented peripheral resistance. Rarefaction may also be functional, only caused by severe capillary vasoconstriction, and therefore reversible. The functional mechanism is thought to be predominant over the anatomical rarefaction when caused by anti-VEGF agents. Finally, VEGF inhibition may induce renal thrombotic microangiopathy; indeed, among the adverse effects of anti-VEGF agents, there is also thromboembolism.

Tyrosine kinase inhibitors sunitinib and sorafenib do also inhibit platelet-derived growth factor (PDGF) receptor (PDGFR), which is involved in angiogenesis as well as VEGFR-2. It is moreover thought that PDGF exerts also a cardiac and vascular protective role. Thus, even if the mechanisms are still unknown, also PDGFR inhibition may contribute to anti-VEGF agent-induced hypertension [15].

Patients at higher risk of developing anti-VEGF agent-induced elevation in BP are usually older, female, with a greater BMI, and with a pre-existing hypertension [37, 39]. The hypertensive adverse effect, at least for bevacizumab, seems to be dose-dependent [35]. Furthermore, it emerged that even certain genetic polymorphisms may play a predisposing role [40, 41]. In particular, genetic variants of VEGF, FIP200, WNK1, KLKB1, and GRK4 may be related with bevacizumab-induced hypertension.

Elevation of BP caused by anti-VEGF agents is rapid [37, 38]. Bevacizumab-induced hypertension usually appears within the first cycle of therapy [35]. An analysis conducted on gynecologic cancer patients found a median onset time of 67 days [42]. In a population of metastatic renal cell carcinoma patients, more than 30% of individuals developed hypertension within 30 days from the beginning of therapy with tyrosine kinase inhibitors [38]. As well as for the onset, this condition is reported to sharply reverse along with the end of the treatment. Timing of onset/offset of anti-VEGF hypertension highlights the importance of a good therapeutic management of this condition. Notably, indeed, anti-VEGF agents are so far used in late-stage cancer diseases, with an expectation of prolonged survival of less than 24 months (mostly less than 12 months). May this be enough time to develop CV complications due to hypertension, i.e., left ventricular diastolic and/or systolic dysfunction, is questionable. Rate of occurrence of heart failure during anti-VEGF therapy is low and more frequent in those with a previous history of hypertension, coronary artery disease, or heart failure [43]. Renal complications (i.e., a severe reduction in glomerular filtration rate) are as well rare [38]. These data suggest that though being a substantial issue in patients on therapy with anti-VEGF agents, hypertension is a manageable adverse effect and, if well treated, rarely causes

complication. Therefore, the primary goal of antihypertensive medicaments should be of reaching acceptable values of BP to allow the patients keep being on chemotherapy.

Another fact must be taken into account when addressing anti-VEGF-induced hypertension. It represents an on-target effect of these drugs; therefore, lot has been speculated regarding the meaning and prognostic value of the development of hypertension. Various studies on metastatic colorectal cancer and metastatic lung cancer patients treated with bevacizumab showed better prolonged free survival, with discordant results regarding overall survival, in those who developed hypertension [34, 44, 45]. In a recent analysis, patients with metastatic colorectal cancer who developed hypertension being treated with bevacizumab had higher overall survival, but this result lost its significativity when patients with preexisting hypertension were excluded from the analysis [46]. In a retrospective analysis, hypertension induced by pazopanib was not related with outcome in patients treated for soft tissue sarcoma [47], while the incidence of hypertension and neutropenia secondary to sunitinib therapy in metastatic renal cell carcinoma was related with a better outcome [34, 48]. This finding was confirmed even by a retrospective review of 50 patients, with both better prolonged free survival and overall survival [49].

This prognostic role on new-onset hypertension due to the anti-VEGF agents' treatment has to be considered when addressing its management. First of all, this concept stresses again what the objective of antihypertensive therapy should be, that is, reaching acceptable BP values to let the patient continue the chemotherapeutic treatment. ACEi and ARBs are the drugs of choice, in particular if proteinuria appears, due to their renoprotective effect. It has been proposed, furthermore, that both these classes of molecules exert also an antineoplastic role, acting on angiotensin 2, which is involved in angiogenesis [50]. Various analyses have showed a better outcome in renal cell carcinoma patients treated with anti-VEGF agents and simultaneously with ACEi or ARBs [51–53]. Dihydropyridine CCB have shown good efficacy, while non-dihydropyridine drugs should be avoided because of their hepatic metabolism involving the cytochrome CYP3A4. In addition, after it was found that levels of endothelin 1 were augmented by anti-VEGF agents, also anti-endothelin drugs were proposed. Moreover, drugs increasing NO have been proposed in this specific context, such as nitrates and the beta-blocker agent nebivolol. However, it should not be excluded that, being hypertension an on-target effect, the way BP values are reduced may influence the anticancer effect of anti-VEGF agents. In fact, it has been shown that NO and its pathway are involved in angiogenesis. There are no clear data nor demonstration that addressing NO may not compromise the anti-angiogenetic, anticancer effect of anti-VEGF agents [34]. In our opinion, antihypertensive medicaments targeting NO should be used cautiously.

Finally, lowering the dose or even interrupting chemotherapy should be considered only if BP values keep being uncontrolled regardless of an optimal antihypertensive treatment.

The Cardiovascular Evaluation Before Starting Antineoplastic Therapies

Cardiotoxicity is a compelling issue. Due to its variety and complexity, definite recommendations for a CV evaluation before starting any antineoplastic treatment are still lacking. At the same time, there is a growing evidence that most patients would need a pre-treatment evaluation and benefit from it. Though specific information to be investigated may depend on clinical circumstances (type of cancer, type of therapy, line of therapy, prognosis), there generally are some common questions to be addressed. The purpose of a CV evaluation is indeed not only to avoid cardiotoxicity but to make possible for the patient to undergo cancer treatment with the *lower possible risk* of cardiotoxicity and, if a cardiac adverse effect presents, to prevent it to cause an early discontinuation of therapy. In other words, the issue of a CV evaluation before starting an antineoplastic therapy should shift from "Is there any contraindication to anticancer therapy?" to "Which is the patient's risk of CV complications

over the entire antineoplastic treatment period, and what would be the best way to manage this eventuality?" [14, 54].

CV risk should be systematically evaluated in all patients with a simple and effective approach, investigating previous CV history, thoracic examination, CV risk factors (glycemic and lipid profile, BP values, renal function), and ECG [27]. The finding of hypertension during this baseline evaluation is of crucial importance.

In particular, specific attention must be paid to two specific categories of hypertensive patients:

1. Those subjects in whom the pre-evaluation has revealed other strong CV risk factors
2. Those going to be treated with anthracyclines or with inhibitors of HER2 or with anti-VEGF agents

These patients would need further investigation, specifically including an echocardiogram, and may benefit from a specialistic cardiologic consultation. Such an approach is paramount, because, as previously reported, an untreated hypertension may seriously compromise the proper course of the antineoplastic therapy.

Hypertensive patients with different profiles may be encountered: those with a previous diagnosis and those newly diagnosed. In the first case, a deeper evaluation is needed to ascertain BP values are on target and to properly consider therapeutic modifications, even for subjects with well-controlled BP on their current therapy. It may be in fact considered for patients undergoing specific regimens (i.e., anthracyclines) to switch from other antihypertensive drugs to those classes known to have a definite cardioprotective effect, such as ACEi or ARBs and second-generation beta-blockers (carvedilol, nebivolol, bisoprolol).

In the case of a newly diagnosed hypertension, the pre-treatment evaluation becomes of significative importance. It must be in fact kept in mind that BP elevation may be a white-coat hypertension or a reactive anxiety disorder, an understandable evenience in patients with a recent diagnosis of cancer. The physician is called to meticously investigate the patient's previous history: did the patient ever measured BP in the past? How frequently? Did BP values were within the normal range? If the patient appears to always have been normotensive, a "reactive" hypertension is probale. In this context, anxiolytic drugs rather than antihypertensive treatments may be more beneficial. Otherwise, the hypothesis of an undiagnosed hypertension should be strongly considered and may be guided by the results from ECG (e.g., signs of left ventricular hypertrophy or strain) and echocardiography. Other actions, such as a Holter BP monitoring or more simply the indication to accurately take a BP daily diary may be reasonably taken into account before starting any treatment.

Patients scheduled to receive treatment with anti-VEGF agents represent a particular population, as reported in the dedicated paragraph. Though for these subjects the aforementioned general approach is basically valid, it is true that it has to be undertaken methodically, since hypertension represents a significantly frequent and severe, but manageable, adverse effect. In this very case, the CV evaluation would benefit from proteinuria screening, a finding that may predict the development of hypertension secondary to anti-VEGF treatment [38].

A fundamental part of this anti-VEGF treatment pre-evaluation is the education of the patient. He/she must be informed that after initiation of therapy, a significative increase in BP values may occur, with a rapid onset (even few days). Practical instruction on how to behave if BP rises must be provided to the patient, in particular advices about the following:

1. How to monitor BP (best condition on how to take the measurement, how frequently to assess BP, which items to use)
2. When to start an antihypertensive drug and when to reinforce the antihypertensive therapy (and how)
3. Which are the values of BP that represent an emergency (usually 180/100 mmHg) and what symptoms must require an immediate medical contact (chest pain, dyspnea, dizziness, headache)

As already said, no definite therapeutic approach for management of hypertension sec-

ondary to anti-VEGF treatment exists. We empirically suggest a step-by-step strategy that may be summarized as follows:

1. If after initiation of anti-VEGF therapy BP values systematically rises over 140/90 mmHg, start immediately with an ACEi/ARBs or CCB therapy.
2. If BP keeps being elevated, add the other drug.
3. If BP keeps being elevated, titrate both drugs.
4. If BP keeps being elevated or if maximum doses of ACEi/ARBs or CCB are already used, add a beta-blocker or a diuretic.
5. If BP keeps being elevated, consider to stop anti-VEGF treatment.

Notably, we believe that if after the first two steps BP values do not reach target values, a cardiologic consultation (if not already performed) is critically needed. Figure 11.1 outlines a sche-

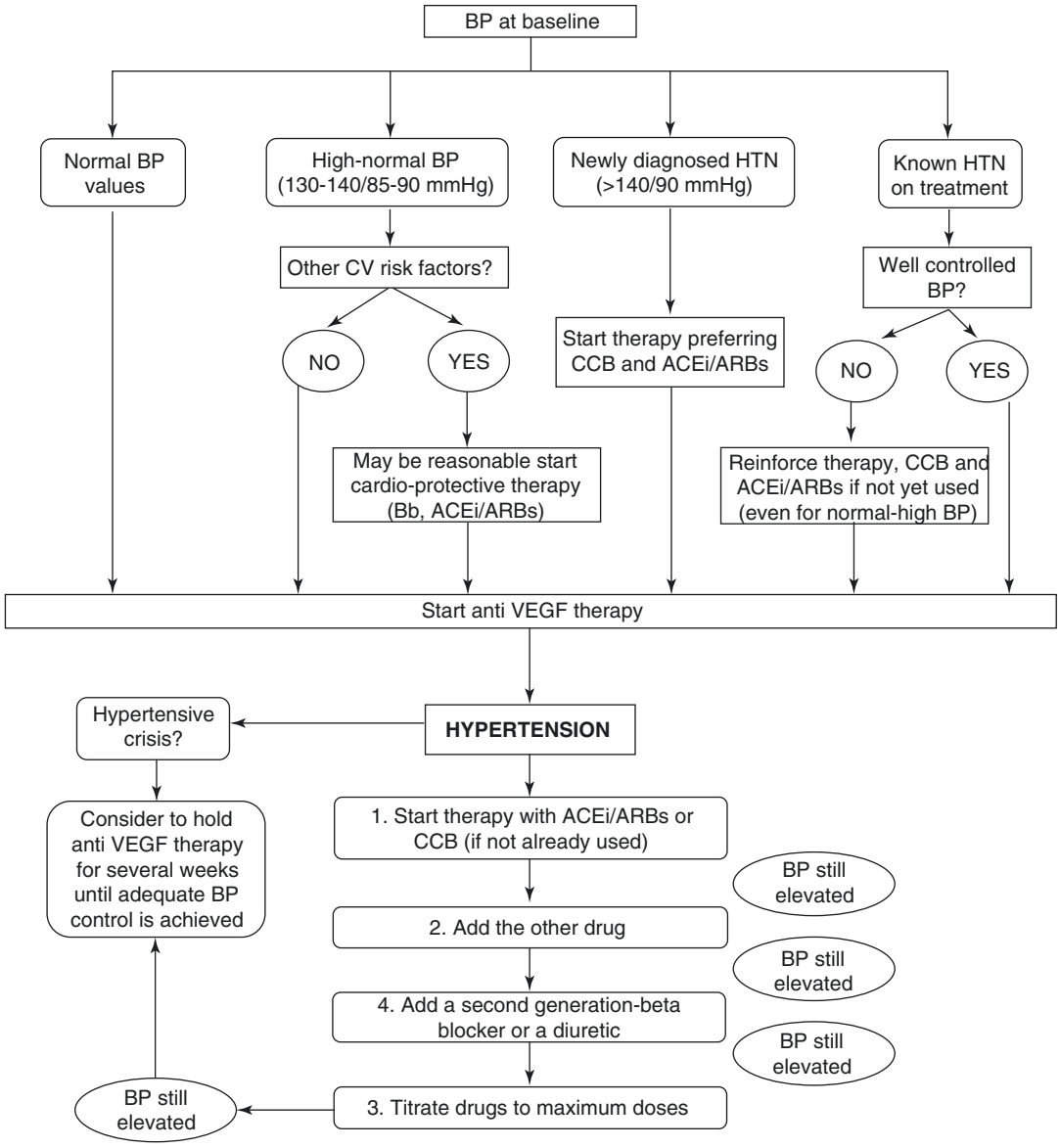

Fig. 11.1 Algorithm for evaluation of blood pressure and management of hypertension before and during anti-VEGF treatment. ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; Bb, beta-blockers; BP, blood pressure; CCB, calcium channel blockers; HTN, hypertension

matized algorithm for the management of hypertension before and during anti-VEGF therapy.

Moreover, patients receiving an anti-VEGF therapy may also benefit from statin treatment. Beyond a concurrent effect on CV risk factors control and on inflammation, it has been reported that statins may also reduce VEGF levels [55].

A final mention is to be given to hypotension. Even cardiac drugs have their side effects and cause changes in sympathetic tone, volemia, heart rate. Cancer itself and antineoplastic treatments are associated with fatigue and hemodynamic alterations. Cardioactive therapies may concur to debilitate the patient on this basis, exacerbating symptoms. While hypertension caused by antineoplastic treatments is widely addressed, secondary hypotension is too often forgotten. We believe that a comprehensive CV evaluation must deal with this issue and be able to modulate cardioactive treatments; it is in fact not unfrequent the needing of suspending or reducing a previous therapy for hypertension in a cancer patient. A similar strategy to that proposed above may be considered—patients should be educated to know how to deal with antihypertension therapy when BP is low. For example, if more than one antihypertensive drug is used, patients may be taught to discontinue one of them when a cutoff value for low BP is registered (i.e., SBP < 100 mmHg).

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Atrial Fibrillation in Cancer

12

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Introduction

Advances in cancer therapy have led to a significant improvement of survival in most types of malignancies over the past few decades. As a result, there is a growing population of cancer survivors, expected to reach 18 million people in 2030 in the USA and a similar number in Europe [1]. Interestingly, cancer survivor studies have shown that although about half of these patients eventually die of cancer, one-third of them actually die of cardiovascular disease [2]. Women diagnosed with breast cancer, one malignancy with particularly high survival rates, have currently a higher risk to die of heart disease than of breast cancer or other malignancies [3]. In addition, adults having survived from childhood cancer have an eightfold higher cardiovascular mortality compared to adults not having experienced cancer during their childhood [4].

Cardiovascular complications in patients with cancer result from the interaction of three main factors: cancer therapy that may confer cardiac or vascular toxicity, cancer itself that may affect the heart directly and mainly indirectly, and the underlying cardiovascular status of patients in terms of coexistent heart disease or cardiovascular risk factors. The cardiovascular spectrum of cancer patients is quite wide, comprising practically every form of cardiac or vascular disease [5]. Arrhythmias represent a significant part of this spectrum, and atrial fibrillation (AF) is one of the main arrhythmias occurring in cancer patients.

Epidemiology

Several studies have documented the relationship between cancer and AF (Tables 12.1 and 12.2). In terms of epidemiology, AF in cancer could be divided into two forms according to whether it occurs during the perioperative period of cancer surgery (perioperative AF) or not. This distinction is important as perioperative AF is characterized by relatively high incidence rates, particularly in patients undergoing pulmonary resection for lung cancer [28].

A recently published study on 833,500 patient records from 26 major healthcare systems in the USA showed that the age-adjusted risk of incident AF in cases with newly diagnosed cancer was 4.4 times higher within the first year of cancer diagnosis and 22–30% higher after the first year [13]. In an earlier large study on 24,000

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Table 12.1 Studies on atrial fibrillation (AF) in patients with cancer

Study	*N*	Type of cancer	AF prevalence or incidence
Guzzetti et al. [6]	456	Colorectal	5.2%
Guzzetti et al. [7]	1317	Colorectal or breast	3.6%
Wilkinson et al. [8]	20,571	Various	18.0% in bisphosphonate group vs 12.7% in controls
Erichsen et al. [9]	11,887	Various	3.2% in bisphosphonate group vs 2.4% in controls
Hu et al. [10]	24,125	Various	2.4% at cancer diagnosis plus 1.8% after cancer diagnosis (new-onset)
Abonowara et al. [11]	136	Thyroid cancer on TSH suppression	10.3%
O'Neal et al. [12]	15,428	Various	18–23% higher adjusted risk
Kim et al. [13]	833,520	Various	4.4-fold higher risk in year 1 of cancer diagnosis; 22–30% higher risk beyond 1 year of cancer diagnosis

Table 12.2 Studies on perioperative atrial fibrillation in patients with cancer

Study	*N*	Type of surgery	AF incidence (%)
Cardinale et al. [14]	233	Pulmonary resection for lung cancer	12
Walsh et al. [15]	174	Colectomy for colorectal cancer	5.4 (pre- and postoperative)
Siu et al. [16]	563	Colectomy for colorectal cancer	4.4
Roselli et al. [17]	604	Pulmonary resection for lung cancer	19
Cardinale et al. [18]	400	Pulmonary resection for lung cancer	18
Salvatici et al. [19]	400	Pulmonary resection for lung cancer	18
Onaitis et al. [20]	13,906	Pulmonary resection for lung cancer	12.6
Nojiri et al. [21]	126	Pulmonary resection for lung cancer	23
Nojiri et al. [22]	80	Pulmonary resection for lung cancer	28
Nojiri et al. [23]	553	Pulmonary resection for lung cancer	5.6
Imperatori et al. [24]	454	Pulmonary resection for lung cancer	9.9
Ciszewski et al. [25]	117	Pulmonary resection for lung cancer	16
Ojima et al. [26]	207	Esophagectomy for esophageal cancer	9.2
Chin et al. [27]	583	Esophagectomy for esophageal cancer	11

patients suffering from various malignancy types, the absolute prevalence of AF at the time of cancer diagnosis was 2.4%, while the incidence of AF after cancer diagnosis was 1.8% [10]. In another large study on 20,500 patients, the reported absolute prevalence of AF ranged between 13% and 18%, depending on whether patients were receiving bisphosphonates or not [8]. Evidence from the "REasons for Geographic And Racial Differences in Stroke" (REGARDS) cohort on nearly 15,500 patients showed a 20% higher adjusted risk for AF (18%, 19%, or 23% higher risk, depending on the adjustment model) in patients with cancer compared to those without cancer [12]. It should be stressed that in the latter analysis, cases with either life-threatening cancer or having received cancer treatment within the previous 2 years had been excluded, and therefore the risk for AF might have been underestimated by this cohort.

A number of studies have addressed the inverse question, that is, the risk of cancer in patients with AF (Table 12.3). In a cohort study of nearly 270,000 Danish patients with new-onset AF, the standardized incidence ratio of cancer (observed divided by expected incidence) was considerably high during the first months after AF diagnosis, reaching 5.1 in the first trimester and dropping to 1.4 during the

Table 12.3 Studies on cancer prevalence or incidence in patients with atrial fibrillation (AF)

Study	*N*	Condition	Cancer prevalence or incidence
Erichsen et al. [29]	28,333 with AF and 283,260 without AF	AF vs no AF	Colorectal cancer: 0.59% in AF vs 0.05% in non-AF
Kim et al. [13]	388,270	New-onset AF	2.6-fold higher risk in year 1 of AF diagnosis; 66% higher risk beyond 1 year of AF diagnosis
Ostenfeld et al. [30]	269,742	New-onset AF	SIR[a] after AF diagnosis: 5.11 in months 0–3 1.38 in months 4–6 1.15 in months 7–12 1.14 in months 13–24 1.11 in months >24
Conen et al. [31]	34,691 women	New-onset AF	48% higher overall risk; 3.5-fold higher in months 0–3 of AF diagnosis; 42% higher beyond year 1 of AF diagnosis

[a]Standardized incidence ratios: observed vs expected cancer incidence

second trimester and to 1.2 during the second semester [30]. In another study on more than 56,500 patients, the incidence of colorectal cancer was 0.6% in patients with AF and only 0.05% in those without AF [29]. Accordingly, an analysis of the Women's Health Study on nearly 35,000 initially healthy women showed that new-onset AF conferred a 48% adjusted risk of cancer beyond 1 year of AF diagnosis [31].

The incidence of AF during the perioperative period ranges between 4.4% and 28% (Table 8.2), depending on the type of surgery and additional risk factors, as described in detail in Table 12.4 [28]. In the largest of studies on cancer-related perioperative AF on nearly 14,000 patients undergoing pulmonary resection, the AF incidence rate was 12.6% [20]. The reported incidence of perioperative AF is generally higher in patients undergoing lung resection (6–28%) compared to those undergoing colectomy (4–5%) or esophagectomy (9–11%; Table 12.2). The vast majority of AF cases seem to occur during the first 3 days after the operation, with one-third of them occurring during the second day, while the incidence rate declines significantly after the third day [18].

Table 12.4 Risk factors for perioperative atrial fibrillation in patients with cancer

Patient-related factors	Advanced age, male gender, history of arterial hypertension, history of paroxysmal AF
Cancer-related factors	Advanced cancer stage, physical status, postoperative tachycardia
Surgery-related factors	Increased duration, complications, need for blood transfusion, extended lung resection in lung cancer, use of colon conduit in esophagectomy
Cardiac indexes or biomarkers	Elevated plasma levels of natriuretic peptides, ectopic beats on ECG, low mean heart rate, low heart rate variability, mitral E/e' ratio >8

Prognosis

In the general population, AF is followed by a twofold increase in the risk of death, a threefold increase in the risk of heart failure, and a fivefold increase in the risk of stroke [32]. It is expected that this would also be the case in patients with cancer. Indeed, in a previously mentioned large study on more than 24,000 patients with newly diagnosed cancer, AF was associated with an almost twofold higher adjusted risk for thromboembolic complications and a sixfold adjusted risk for heart failure [10]. In contrast, in a large database of 10,358 patients with AF, half of whom were receiving anticoagulation with vitamin K antagonists (VKA), cancer was not followed by higher stroke incidence, regardless of VKA therapy [33]. On the other hand, the presence of active cancer was associated with a tenfold higher adjusted 30-day mortality in patients with newly diagnosed AF [34].

In what concerns the prognostic impact of perioperative AF, it was identified as an independent predictor of 5-year mortality in 454 patients who underwent pulmonary lobectomy for lung cancer [24]. In addition, perioperative AF was associated with 2.5-fold higher 1-year mortality and 50% higher long-term mortality in 583 patients undergoing esophagectomy for esophageal cancer [27].

Pathophysiology

According to epidemiological evidence, there seems to be a bidirectional relationship between AF and cancer, as the one increases the risk for the other (Fig. 12.1). This is partly explained by the common pathogenetic mechanisms and risk factors that the two conditions share, such as aging, systemic inflammation, smoking, or obesity [28, 35]. At the same time, cancer may lead to complications that are risk factors for AF, as explained in more details below, and vice versa: AF may cause conditions that may in turn predispose to cancer [35].

Cancer-related complications may predispose to AF. Such complications include paraneoplastic manifestations like hyperparathyroidism or autoimmunity, autonomic nervous system imbalance caused by pain, vomiting or other forms of physical or emotional stress, as well as electrolyte or other metabolic disorders [28].

Cancer may further cause atrial fibrillation among other cardiac manifestations directly by invading the heart in the form of primary or, more frequently, metastatic tumors or tumors expanding from adjacent structures, although the cases of cardiac tumors causing heart disease are rather rare.

On the other hand, cancer therapies may cause arrhythmias, including atrial fibrillation either indirectly through other forms of cardiotoxicity, such as cardiomyopathy or myocardial ischemia, or electrolyte and metabolic disorders or directly by causing a pro-arrhythmic effect. A wide spectrum of anticancer medical therapies has been associated with AF. These drugs include alkylating agents, such as cisplatin or cyclophosphamide; anthracyclines; antimetabolites, such as 5-fluorouracil or gemcitabine; taxanes; topoisomerase II inhibitors, such as etoposide and vinca alkaloids; targeted therapies, such as rituximab or small molecule tyrosine kinase inhibitors (sorafenib, sunitinib, etc.); biological agents, such as interferon or interleukin-2; and supporting therapies, such as bisphosphonates [5]. In addition, surgical resection of tumors, particularly pulmonary resection for lung cancer, is frequently followed by AF, as described previously in detail [28].

Treatment

There are no cancer patient-specific strategies for the management of AF, and all modalities used in noncancer patients are applicable [28]. As in noncancer patients, the medical history and coexistent conditions along with patient preferences should always be taken under consideration. In

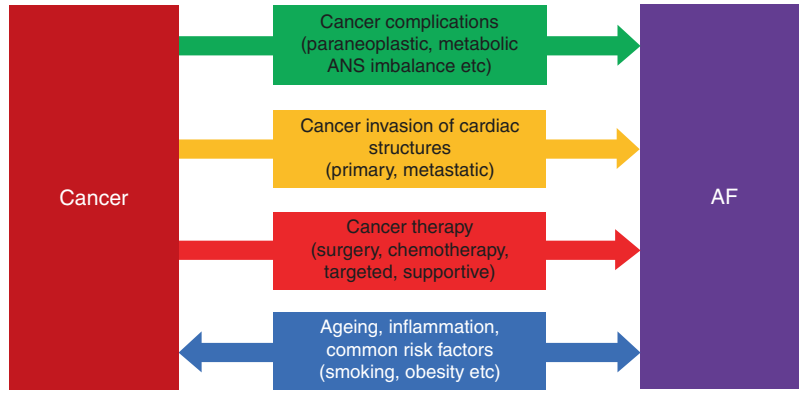


Fig. 12.1 Pathophysiology of atrial fibrillation (AF) in patients with cancer

addition, cancer status and prognosis should also be considered in treatment decisions, with symptomatic interventions being more suitable for end-stage metastatic cancers and more sustainable or disease-modifying interventions being favored in patients with good prognosis and reasonable life expectancy.

A rhythm control strategy seems to be appropriate for patients with recurrent paroxysmal AF and/or other cardiovascular comorbidities and a good cancer prognosis, while a rate control approach is more suitable for patients with end-stage metastatic disease on palliative care [28]. As in noncancer AF patients, cardioversion to sinus rhythm may be accomplished either pharmacologically or electrically. In terms of pharmacological cardioversion, results from a small retrospective study favor the use of ibutilide in cancer patients [36]. However, the QT prolongation effect of ibutilide and several other antiarrhythmic agents should be taken under consideration, particularly in patients receiving concomitant therapies that also prolong the QT interval including anticancer agents such as arsenic trioxide and tyrosine kinase inhibitors (especially vandetanib and vemurafenib) or supportive therapies such as antiemetics, antibiotics, or psychotropes, as well as in patients with concomitant electrolyte disturbances that may be common in cancer [5]. Radiofrequency ablation and the more recently introduced cryoablation are suitable for patients with symptomatic paroxysmal AF despite antiarrhythmic therapy and a reasonable cancer-dependent life expectancy. Left atrial appendix closure may be an option for patients with high thromboembolic and bleeding risk and also a reasonably good prognosis [28].

Perioperative AF

Concerning the management of perioperative AF in cancer, two small clinical studies have reported positive results with the use of landiolol, a short-acting beta-1 adrenergic receptor blocker, but, in general, rate control and cardioversion to sinus rhythm follow the rules that apply in noncancer patients [23, 26]. On the other hand, the effective prevention of perioperative AF would be of interest, since it seems to confer a worse prognosis in cancer survivors, as previously discussed [24, 27]. Amiodarone, administered at 300 mg IV immediately after surgery followed by 600 mg orally twice daily for the first 5 postoperative days, conferred a 23% reduction in AF incidence in patients undergoing pulmonary resection for lung cancer [37]. A more individually tailored approach has been suggested by another group of investigators: they used preoperative NT-proBNP to identify patients at increased risk of developing postoperative AF and randomized those patients either to metoprolol or losartan; both drugs were associated with a reduction in the perioperative risk of 70–80% (risk ratio, 0.19 [0.09–0.37] for metoprolol and 0.29 [0.16–0.52] for losartan) [38].

Anticoagulation

Anticoagulation represents the most challenging issue concerning the management of AF in patients with cancer because of the following reasons [28]:

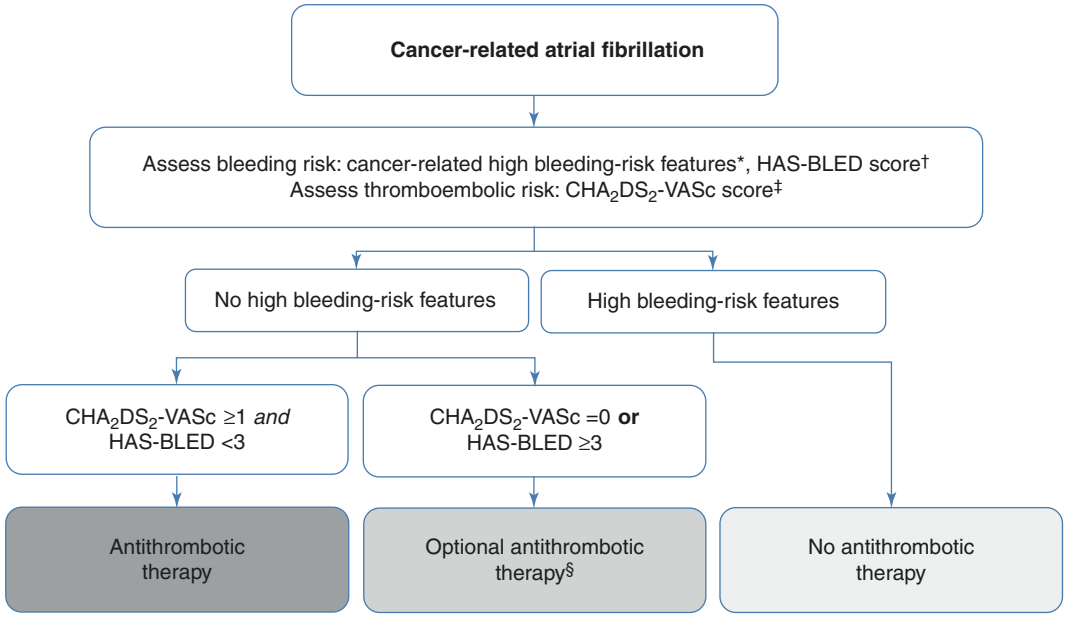
- Cancer itself may be associated with an increased risk of thromboembolic complications. This increased risk is related to both specific types of malignancies, such as gastrointestinal tract adenocarcinomas, pancreatic, ovarian, lung or hepatocellular cancer, and to certain cancer therapies such as platinum compounds, pyrimidine analogues, anti-angiogenetic factors or to supportive therapies such as erythropoietin or granulocyte colony stimulating factors. As a result, anticoagulation may be needed even in patients with a typically low AF-related thromboembolic risk in the presence of additional thromboembolic risk factors related to certain types of malignancies or cancer therapies.
- Cancer may also be associated with an increased risk of bleeding, as in cases with intracranial primary or metastatic disease, hematologic malignancies with coagulation defects, extensive metastatic hepatic disease, or in the case of thrombocytopenia induced by

cancer therapies. Therefore, antithrombotic therapy may be contraindicated in the presence of the aforementioned bleeding risk factors even in patients with typically high AF-related thromboembolic risk.

- Thromboembolic and hemorrhagic risk assessment tools, such as the widely used CHA_2DS_2VASc and HASBLED, respectively, have not been validated for cancer patients. Therefore, anticoagulation cannot be solely based on the use of these and other risk calculators.

The recently published position paper of the European Society of Cardiology on cancer treatments and cardiovascular toxicity suggests that cancer patients with AF can be started on anticoagulation if the CHA_2DS_2VASc score is 2 or higher and the platelet count is higher than 50,000/mm^3, stressing at the same time the need for an individually tailored approach [5]. A previously published algorithm suggested the use of CHA_2DS_2VASc and HASBLED scores in combination with cancer-related bleeding risk factors to guide the decision to anticoagulate or not (Fig. 12.2) [28].

There is no strong evidence favoring the use of certain anticoagulating factors over the others. Low-molecular-weight heparins (LMWH), vitamin K antagonists (VKA), and new oral antico-



*Intracranial tumor, hematologic malignancies with coagulation defects, cancer therapy-induced thrombocytopenia, severe metastatic hepatic disease etc.
†HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly
‡CHA_2DS_2-VASc = Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex (female)
§Antithrombotic therapy may be considered in high thromboembolic risk associated with certain cancers (e.g., pancreatic, ovarian, lung, primary hepatic) or cancer therapies (e.g., cisplatin, gemcitabine, 5-fluorouracil, erythropoietin, granulocyte colony stimulating factors).

Fig. 12.2 Proposed algorithm for the guidance of antithrombotic therapy in patients with cancer and atrial fibrillation. (Reprinted from Farmakis et al. [28]. With permission from Elsevier)

agulants (NOAC) are all viable options. LMWH constitute the treatment of choice for deep vein thrombosis in cancer patients. Heparins have been deemed to possess some poorly understood antineoplastic properties [39], while LMWH have been shown to prolong survival in cancer patients with or without venous thromboembolism [40, 41]; however, their use for thromboembolic prevention in AF is limited in the general population. VKA seems to be the preferred treatment in cancer patients with AF, according to a cohort in study, in which the presence of cancer favored the use of VKA [42], and they can further be easily monitored using INR. However, VKA bear two important drawbacks, the need for continuous monitoring and the multiple interactions with several drugs including a lot of anticancer agents that may either increase or decrease VKA's activity [43].

New oral anticoagulants, on the other hand, have not been sufficiently studied in AF patients with cancer, as those patients had largely been excluded from the corresponding clinical trials. Limited evidence from secondary analyses of NOAC trials and some additional clinical studies show that the use of NOAC in cancer patients is as safe and effective as in noncancer patients [44–47]. More specifically, in the seminal study of apixaban for AF, the ARISTOTLE trial, a total of 1236 of patients (7%) had cancer, including 157 with either active cancer or cancer treated within a year; apixaban had similar efficacy and safety as warfarin in patients with and without cancer. This drug seemed to confer an even greater benefit in patients with active or recently treated cancer [45]. Similarly, in a secondary analysis of the ENGAGE AF-TIMI 48 trial, the seminal study of edoxaban in AF, which included 1,153 patients with cancer, edoxaban had a similar efficacy in preventing stroke and systemic embolic events in patients with and without cancer and had a similar risk of major bleeding [46]. Finally, in a small study of 163 patients with active cancer and AF, rivaroxaban had similar efficacy and safety as that documented by its seminal study in AF, the ROCKET-AF [44]. Drug-to-drug interactions may also be of concern for NOAC, which should be used with caution in cancer patients receiving therapies that affect either P-glycoprotein in the case of all four NOAC or cytochrome CYP3A4 in the case of rivaroxaban, apixaban, and edoxaban. Agents that inhibit P-glycoprotein or CYP3A4 and therefore increase plasma levels of NOAC include cyclosporine, tacrolimus, and TKI such as lapatinib, sunitinib, or imatinib [47]. In contrast, agents that induce P-glycoprotein or CYP3A4 activity and therefore decrease the plasma levels of NOAC include dexamethasone, doxorubicin, and vinblastine [47]. Impaired renal function may also be of concern for the use of NOAC in patients with cancer, as these agents are contraindicated in severe renal dysfunction.

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13 Management of QT Prolongation Induced by Anticancer Drugs

Nicola Maurea, Rolando Paciello, Carmela Coppola, and Dimitrios Farmakis

Prolongation of Corrected Qt (Qtc) and Cardiac Arrhythmias

The QT interval, i.e. the time between the start of the Q wave and the end of the T wave, represents the electrical depolarization and repolarization of the ventricles (Fig. 13.1). Cardiac repolarization abnormalities can cause prolongation of the QT interval, which can also be triggered by drugs that affect subunits of voltage-gated channels. QT prolongation, aka "long QT syndrome" (LQRS), can be associated to a specific ECG polymorphic form of ventricular tachycardia designated *torsades de pointes* (TdP), which is characterized by QRS complexes that oscillate around the isoelectric and differ in morphology and continuous voltage. As shown in Fig. 13.2, correction formulae have been devised to improve the accuracy of QT measurement (QTc) [1–6]. For example, correction according to Fridericia's formula improves the accuracy of QT measurement in cases of heart rates higher than 100 beats per minute (bpm) or lower than 60 bpm. The National Cancer Institute (NCI) has classified the QT prolongation associated with anticancer drugs into four grades: grade 1, QTc 450–480 ms; grade 2, QTc 481–500 ms; grade 3 QTc > 501 ms on at least two separate electrocardiograms; and grade 4 QTc > 501 ms or a change of >60 ms from baseline and TdP, polymorphic ventricular tachycardia, or signs or symptoms of severe arrhythmia [7].

Several factors can cause QT prolongation in patients with cancer [8, 9], namely, anticancer drugs (arsenic trioxide [ATO], ceritinib, crizotinib, dasatinib, nilotinib, lapatinib, panobinostat, pazopanib, romidepsin, sorafenib, sunitinib, vandetanib, vemurafenib, and vorinostat), coexisting risk factors (hypothyroidism, congenital long QT syndrome, left ventricular dysfunction, myocardial ischemia), concomitant treatments (antidepressants, antiemetics, antibiotics, antipsychotics, antifungal agents, antihistamines, and methadone), and side effects associated with cancer therapy (nausea, vomiting, dehydration followed by electrolyte imbalances such as hypokalaemia, hypomagnesaemia, hypocalcaemia, kidney failure, liver dysfunction, and poorly controlled diabetes).

The classes of anticancer drugs associated with QTc prolongation are as follows: ATO, anthracyclines, angiogenesis inhibitors, epidermal growth factor receptor 2 (HER2/ErbB2) inhibitors, Abelson murine leukaemia viral oncogene homo-

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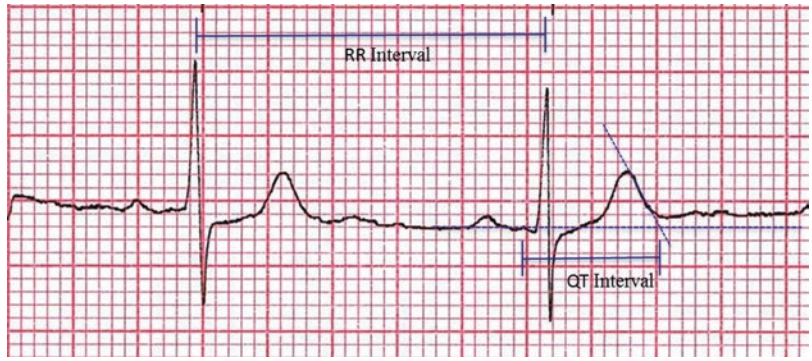


Fig. 13.1 Tangent method for QT interval measurement. (Reprinted from Coppola et al. [10]. With permission from Elsevier)

$$QTc = \frac{QT}{\sqrt{RR}} \quad \text{Balzett}$$

$$QTc = RR^{1/3} \quad \text{Fridericia}$$

$$QTc = QT + 0.154(1 - RR) \quad \text{Framingham}$$

$$QTc = QT + 1.75(FC - 60) \quad \text{Hodges}$$

Fig. 13.2 Correction formulas to improve QT measurement. (Reprinted from Coppola et al. [10]. With permission from Elsevier)

log 1 (ABL1) inhibitors, histone deacetylase (HDAC) inhibitors, and other various agents.

In the clinical setting, data should be collected using the "tangent" method to measure the QT interval, the Bazett and Fridericia formulae should be used for heart rate correction (Fig. 13.2), and the risk factors of electrolyte abnormalities (potassium and magnesium in particular) should be identified and corrected. Concomitant drug treatment that prolongs the QT interval (e.g. antiarrhythmic agents, diuretics, antianginal, antifungals, antibiotics, antiemetics, psychotropic drugs, etc.) should be evaluated [8–12]. Figure 13.3 shows the algorithm for the management of QT prolongation during antineoplastic therapy used in our centre [12].

Angiogenic Inhibitors

Angiogenesis inhibitors, which block vascular endothelial growth factor (VEGF) and its receptors, are multi-target agents and consequently exert cardiotoxic effects [13, 14]. In particular, vandetanib and sunitinib have often been associated with QT prolongation [14].

Vandetanib

Besides being associated with QT prolongation, vandetanib has been associated also with TdP and sudden death [14–16]. Moreover, a meta-analysis of nine phase II or III clinical studies, for a total of 2,188 cancer patients (thyroid, breast, and lung cancer), showed that vandetanib treatment resulted in a significant increase in the overall incidence and risk of QTc prolongation [16]. Importantly, hypocalcaemia and hypomagnesaemia should be corrected before administering vandetanib. Moreover, an ECG should be performed 2, 4, 8, and 12 weeks after initiation of treatment and every 3 months thereafter. Electrolyte and calcium levels should be monitored during treatment. Vandetanib is not advisable in patients with a QTc > 480 ms. Patients in whom QTc interval prolongation exceeds 500 ms during treatment should stop the medication until the QTc interval returns to values less than 450 ms, after which the drug can be re-administered at a reduced dose [17].

Pazopanib

Pazopanib is a multi-targeted tyrosine kinase inhibitor (TKI) against VEGFRs, PDGFRs, and c-kit receptors [18] that is approved for the treatment of advanced renal cell carcinoma and for subtypes of sarcoma [19, 20]. It causes QT prolongation (>500 ms) in 2% of cases and is associated with a <1% incidence of TdP [21]. Consequently, it should be used with caution in patients affected by heart disease and also in patients taking antiarrhythmics or other drugs known to prolong the QT interval.

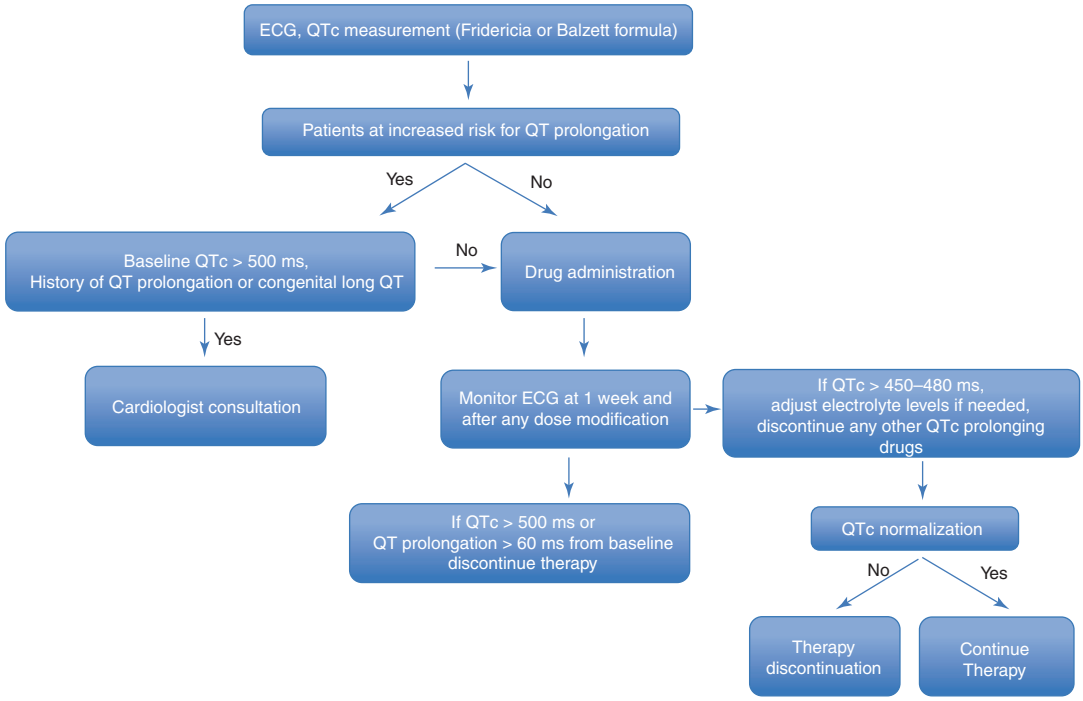


Fig. 13.3 Assessment and management scheme during chemotherapy with potential QTc effect. (Reprinted from Coppola et al. [10]. With permission from Elsevier)

Sunitinib and Sorafenib

The multi-target TKIs sunitinib and sorafenib and sorafenib are potent inhibitors of VEGFRs, PDGFRs, and c-kit and are used in the second-line treatment of renal cancer and hepatocellular carcinoma [22] that has been associated with fatal adverse cardiovascular effects [23–26]. While sunitinib has a dose-dependent effect on the QTc interval, the effect of sorafenib on QTc appears modest and is unlikely to be of clinical relevance [1, 14, 27–29]. An ECG should be performed at baseline and during treatment in patients on sunitinib or on other potential QTc-prolonging drugs [27, 28].

ErbB2 Inhibitors

Lapatinib

Lapatinib, a TKI administered in patients with HER2-positive metastatic breast cancer, is the only ErbB2 inhibitor associated with QTc prolongation [30]. Caution should be exercised in administering lapatinib in patients affected by conditions that may favour QT prolongation, i.e. electrolyte disorders (hypokalaemia and hypomagnesaemia) and congenital (LQT) and concomitant administration of QT prolonging drugs [31]. In line with the Italian Drug Agency, we recommend that hypokalaemia and hypomagnesaemia be corrected and ECG performed with QT measurement in candidates for lapatinib treatment (Fig. 13.4) [30].

ABL Inhibitors

Dasatinib and Nilotinib

Dasatinib and nilotinib are the two BCR-ABL inhibitors that have been approved by the US Food and Drug Administration for the treatment of patients affected by chronic myeloid leukaemia. These second-generation multi-target TKIs are associated with QT prolongation [2].

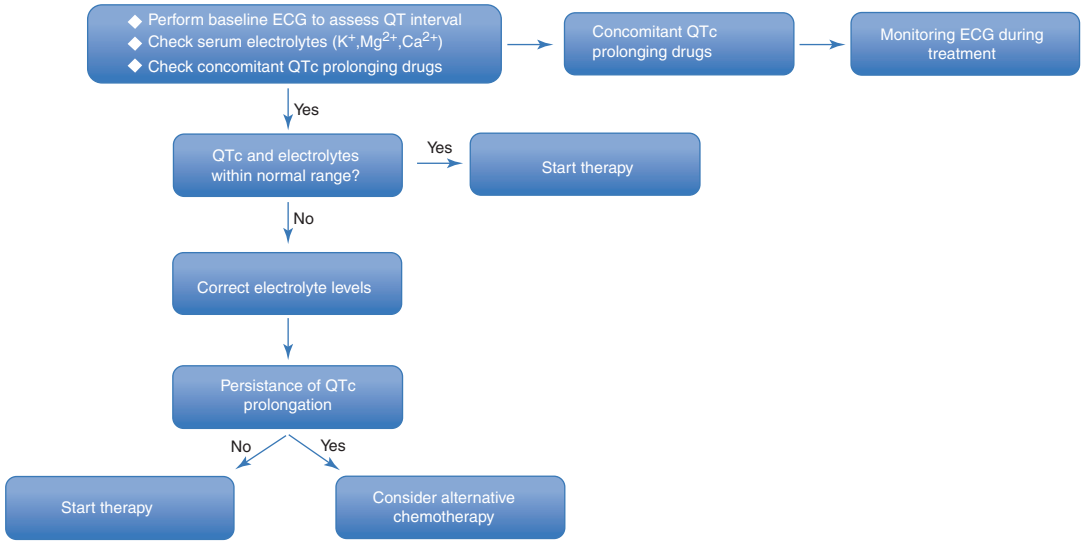


Fig. 13.4 QT monitoring during treatment with lapatinib. (Reprinted from Coppola et al. [10]. With permission from Elsevier)

Recommendations for the Use of Nilotinib and Dasatinib [32, 33]

- If QTc > 480 ms and serum electrolytes are not within normal limits, correct electrolyte abnormalities if present, and check the possible use of QT prolonging drugs.
- If QTc > 480 ms and serum electrolytes are within normal limits, repeat the ECG and re-evaluate serum electrolyte levels 7 days later.

After this time:

- If QTc > 480 ms, discontinue treatment, correct the dystonia, and check for the concomitant use of QT prolonging drugs.
- If QTc returns <450 ms, resume the drug at the previous dosage.
- If QTc returns to 450–480 ms, reduce the dose to 400 mg once daily.
- If QTc interval is >480 ms even after a dose reduction to 400 mg once a day, treatment must be interrupted.

Histone Deacetylase Inhibitors

In vivo and in vitro studies have demonstrated that histone deacetylase inhibitors (HDACi), a family of nuclear proteins, affect DNA by blocking the activity of histone deacetylase and exert multiple effects in all cell types, namely, growth arrest, cell differentiation interference, and induction of apoptosis of malignant cells [34]. Vorinostat and romidepsin, two HDACi approved in the USA for the treatment of cutaneous T-cell lymphoma, can lead to ECG changes and QTc prolongation [34–36]. Consequently, routine ECG monitoring is recommended for both drugs. Importantly, they must be used with caution in patients affected by cardiovascular disease or congenital long QT syndrome, and in patients taking drugs that prolong the QTc or that inhibit cytochrome P450 (CYP450). In the latter case, potassium and magnesium levels should be closely monitored [37, 38].

Panobinostat is used to treat refractory multiple myeloma and can exert a cardiotoxic effect, including QTc prolongation [39]. Also in the case of treatment with panobinostat, the patient's ECG features and potassium and magnesium levels should be monitored. Panobinostat is contraindicated in patients with a recent history of myocardial infarction or unstable angina and in patients with a QTc interval > 480 ms or significant ST- or T-wave abnormalities [38, 40]. Figure 13.5 shows the algorithm used in our centre for the management of panobinostat-induced prolongation of the QTc.

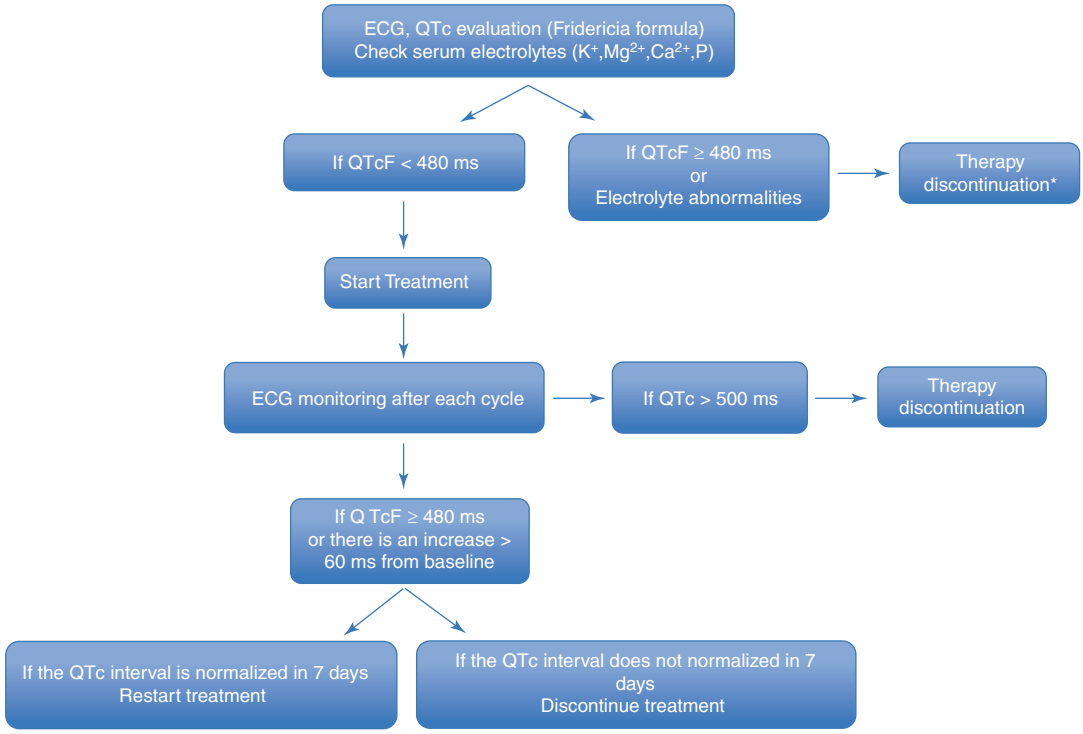


Fig. 13.5 Algorithm for the management of QT prolongation induced by panobinostat. (Reprinted from Coppola et al. [10]. With permission from Elsevier)

Other Agents Associated with LQRS

Arsenic Trioxide

Arsenic trioxide is an effective agent in the treatment of patients with acute promyelocytic leukaemia. It has been associated with QT prolongation and can lead to TDP, which is a potentially fatal ventricular arrhythmia [41–44]. The risk of TdP is associated with the following conditions: co-administration of drugs known to prolong the QT interval, a history of TdP, pre-existing QT interval prolongation, and other conditions that lead to hypokalaemia or hypomagnesaemia [45, 46]. However, it can be safely administered in patients with acute promyelocytic leukaemia provided patients undergo ECG monitoring and evaluation of electrolyte levels.

Vemurafenib

Vemurafenib is an oral inhibitor of the mutant BRAF protein (V-raf murine sarcoma viral oncogene homolog B1) that has been approved for the treatment of metastatic melanoma due to the BRAF V600E mutation [47]. It is associated with QTc prolongation. Consequently, ECG and electrolyte monitoring are recommended before vemurafenib treatment and after any dose modification. In patients undergoing vemurafenib treatment, ECG should be carried out at baseline, after 15 days of treatment, monthly during the first 3 months of treatment and every 3 months thereafter, and more frequently if clinically indicated. Treatment must be interrupted if the QTc interval exceeds 500 ms, and any electrolyte abnormality should be corrected [31]. A dose of 720 mg vemurafenib can be taken twice a day (or 480 mg twice daily if the

dose had been lowered). In case of a third manifestation of QT > 500 ms, treatment suspension is recommended.

Ceritinib and Crizotinib

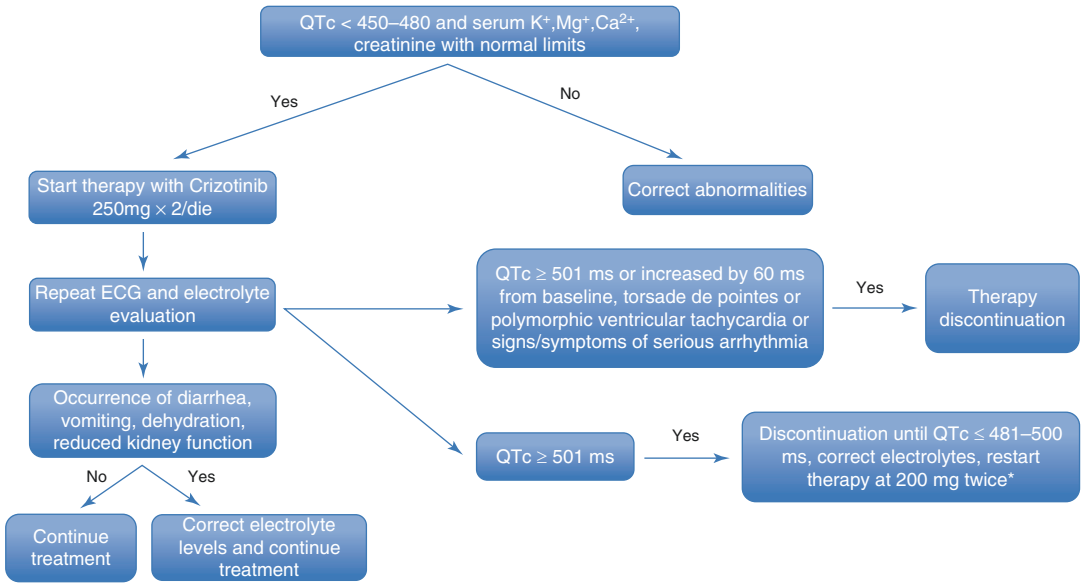
Ceritinib and crizotinib, which are oral inhibitors of anaplastic lymphoma kinase, are approved for the treatment of advanced cancer and metastatic non-small cell lung cancer [48, 49]. In a study of 304 patients treated with ceritinib, the QTc interval exceeded 500 ms in only one patient (<1%). In a later study, an increase of the QTc interval of 60 ms from baseline was observed in only 3% of 255 patients treated with ceritinib [50, 51]. Suspension of treatment and dose reduction are recommended only if QTc prolongation exceeds 500 ms. Also crizotinib is associated with QTc prolongation and with a feasible risk of a ventricular tachyarrhythmia event. Figure 13.6 shows the algorithm for the management of crizotinib used in our centre.

Immunotherapy

QT prolongation can result from the block of the rapidly activating delayed rectifier potassium channel [52, 53]. Nivolumab, a fully human IgG4 (S228P) monoclonal antibody that binds and blocks the programmed cell death 1 (PD-1) receptor, is used to treat patients affected by melanoma, non-small cell lung cancer, renal cell carcinoma, relapsed or refractory Hodgkin lymphoma, and other neoplasias [53]. It was recently reported that nivolumab did not have any clinically meaningful effect on QTc interval when administered at doses up to 10.0 mg/kg [53].

PARP Inhibitors

Polymers (ADP-ribose) polymerases 1 and 2 (PARP-1 and PARP-2) are essential components of the base excision repair pathway that is involved in the repair of DNA-induced radiation



*In case of further appearance of toxicity CTCAE (Common Terminology Criteria for Adverse events) grade > 3, permanently discontinue treatment

Fig. 13.6 QT monitoring during treatment with crizotinib. (Reprinted from Coppola et al. [10]. With permission from Elsevier)

damage and damage caused by methylating agents. PARP inhibition is an effective strategy with which to treat cancer associated with homologous recombination deficiency (e.g. BRCA mutations) [54].

Rucaparib

Rucaparib, the first PARP inhibitor to be approved, is used in the treatment of patients with a deleterious BRCA mutation associated with advanced ovarian cancer who have been treated with two or more chemotherapy regimens (Study 42, ClinicalTrials.gov NCT01078662) [55, 56]. At a dose of 600 mg orally twice daily as monotherapy, rucaparib had no clinically relevant effect on QTc prolongation [57].

Niraparib

The PARP inhibitor niraparib is indicated in the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer [58]. This compound is not associated with any clinically relevant effect on QTc prolongation [59].

Veliparib

Veliparib (ABT-888) is an orally bioavailable potent PARP inhibitor that does not exert any clinically relevant effect on QTcF prolongation [60].

CEP-9722

CEP-9722 is a prodrug of CEP-8983, which is a potent PARP-1/PARP-2 inhibitor. It has been demonstrated that CEP-9722 at a dose of 750 mg/day was the highest dose that was adequately tolerated in combination with temozolomide at a dose of 150 mg/m^2. Dose-limiting toxicities were nonhematological in nature. Pharmacokinetic and pharmacodynamic results indicate that further formulation development and a twice-daily dosing schedule should be considered [61].

Olaparib

Olaparib is an FDA-approved drug for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. When used at a low dose (100 mg twice daily) and at a maximum tolerated dose (400 mg twice daily), olaparib did not produce any significant ECG changes versus baseline [62].

CDK4/CDK6 Inhibitors

Cyclin-dependent kinases (CDKs) 4/6 are members of the protein kinase family that regulates the cell cycle during G1/S transition. The latter event is impaired in many cancer cells due to the deregulated expression of D-type cyclins. CDK inhibitors prevent the formation of an active kinase complex thereby inhibiting their activity.

Ribociclib

Ribociclib is a cyclin-dependent kinase 4 and 6 (CDK4/CDK6) inhibitor used to treat postmenopausal women hormone receptor-positive, human epidermal receptor 2-negative advanced breast cancer [63]. The QT prolongation experienced by patients was found to be reversible and managed by dose interruptions and reductions, without any clinical consequences [64]. It is recommended that patients undergo ECG examination at baseline, on day 14 of cycle 1 and at the onset of cycle 2, as well as monitoring of serum electrolytes (i.e. potassium, magnesium, calcium, and phosphorous) before treatment and at the start of the

first six cycles, in order to correct any existing electrolyte abnormalities [65]. Depending on the severity of QT prolongation, it may be necessary to interrupt the treatment, reduce the dose and/or discontinue the treatment [65].

Palbociclib

Palbociclib is a reversible, highly selective, CDK4/CDK6 inhibitor that has been approved by the FDA to be used in combination with letrozole for the treatment of oestrogen receptor-positive advanced breast cancer [66, 67]. QTc interval prolongation was not observed in patients treated with this drug at the recommended dosing regimen [68, 69].

Abemaciclib

Abemaciclib is a CDK4/CDK6 inhibitor used to treat advanced and metastatic breast cancers [70]. The Monarch study evaluated the safety and efficacy of this drug, used both as monotherapy and with fulvestrant, in metastatic breast cancer in 132 women [71, 72].

Conclusions

A large body of evidence shows that anthracyclines used in combination with other drugs, namely, trastuzumab and ErbB2 inhibitors, exert cardiotoxic effects albeit with a low incidence of QT prolongation. Clinical trials are now underway to evaluate how TKIs and other new drugs can affect the QT interval.

To achieve optimal management of QT prolongation, it is necessary to maximize prevention, optimize QT interval measurements, and modify and/or discontinue the therapy in relation to the degree of QT lengthening. In addition, a specific algorithm for each drug or class of drug would assist the physician in the treatment and management of oncologic patients. Ideally, such algorithms should contain information about the management of patients based on the presence of correctable factors, for example, electrolyte imbalance, hypothyroidism, and concurrent use of QT-prolonging drugs. Finally, cardiologists or intensivists who are experts in the metabolism of cancer drugs and their half-life should be involved in the management of major arrhythmias and TdP.

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14 Pulmonary Hypertension Induced by Anticancer Drugs

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Introduction

Among the manifestations of anticancer drug-induced cardiotoxicity involving the pulmonary circulation, the development of pulmonary hypertension (PH) is a rare but well-recognized possible complication of childhood chemotherapy and bone marrow transplantation (BMT) for leukemia [1], while other chemotherapeutic agents such as alkylating drugs (mitomycin C, cyclophosphamide) can determine progressive obstruction of small pulmonary veins rather than the distal pulmonary arterioles, thus leading to pulmonary veno-occlusive disease (PVOD) [2]. The tyrosine-kinase inhibitor (TKI) dasatinib, used as second-line treatment for chronic myelogenous leukemia, represents the most interesting example of a chemotherapeutic drug that can induce PH [3]. When the increase in pulmonary pressure meets the hemodynamics criteria for precapillary PH (defined as mean pulmonary artery pressure of >25 mmHg at rest, with pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistance >3 wood units in the absence of other causes of precapillary PH such as lung diseases, chronic thromboembolic PH, or other rare diseases), this condition is diagnosed as drug-induced pulmonary arterial hypertension (PAH), and it is categorized in the group 1 of the clinical classification for PH [4] (Table 14.1).

PAH, regardless of the etiology, is a rare condition that is often difficult to diagnose because of the nonspecific symptoms in the early stage of the disease but has a serious and progressive course, leading to the development of right heart failure and ultimately death [4, 5]. The latest guidelines for diagnosis and treatment of PH classified as *likely* the risk level of dasatinib to induce PAH, while *possible* the risk associated with some chemotherapeutic agents such as alkylating agents (mitomycin C, cyclophosphamide) [4]. Theoretically, PH with unclear or multiple causes may develop in patients with chronic myeloid leukemia per se, independently from chemotherapeutic drugs [6, 7]. However, data from the French PH Registry clearly showed that all incident cases of PH reported in chronic myeloid leukemia occurred only in patients

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Table 14.1 Summary of the main antineoplastic treatments that can induce pulmonary vascular toxicity

Antineoplastic treatment	Clinical feature	Mechanism
Bone marrow transplantation	PAH, PVOD	Endothelial dysfunction
Mitomycin C	PVOD	Endothelial dysfunction/VEGF receptor inhibition
Bleomycin	PH secondary to pulmonary fibrosis	Oxidative damage, relative deficiency of the deactivating enzyme bleomycin hydrolase, genetic susceptibility, and production of inflammatory cytokines
Cyclophosphamide	PVOD, rarely PAH	Endothelial dysfunction
Dasatinib	PAH	Inhibition of tyrosine kinases implicated in cellular proliferation/pulmonary vascular balance

Abbreviations: *PAH* Pulmonary Arterial Hypertension, *PVOD* Pulmonary Veno-Occlusive Disease, *PH* Pulmonary Hypertension, *VEGF* Vascular Endothelial Growth Factor

treated with dasatinib. Furthermore, a direct link between dasatinib and PH was demonstrated by the clinical and hemodynamic improvement observed after switching dasatinib with another TKI, like nilotinib [3].

As mentioned, cyclophosphamide and other alkylating agents pulmonary vascular toxicity involves predominantly small venules, in the form of PVOD. This condition represents the most severe form of pulmonary hypertension and unfortunately lacks effective pharmacological treatment so far. PVOD is a rare form of PH typically characterized by progressive obstruction of small pulmonary veins, due to a widespread fibrous intimal proliferation of veins and venules, often associated with pulmonary capillary dilatation and proliferation [8]. Its diagnosis is quite a challenge, and it is often misclassified as idiopathic PAH. Chemotherapy-induced PVOD has a fatal course in most of the cases, even if few case reports suggest that specific treatment with the pulmonary vasodilator endothelin receptor antagonist may induce a favorable response [9, 10]. The pathophysiological mechanisms of PVOD are poorly understood. Limited case reports or case series of PVOD induced by polychemotherapeutic treatment have been reported in the literature [10, 11]. Even if a clear relationship between a specific drug and PVOD is difficult to establish because of the use of several combinations of drugs in chemotherapeutic regimens, basing on observations from the literature, it has been demonstrated that a key role in the development of this adverse toxicity is played by alkylating agents and in particular by mitomycin C and cyclophosphamide but also bleomycin and carmustine [2, 12–14]. Moreover, also BMT is considered a risk factor for PAH and PVOD [15, 16].

Mechanisms of Pulmonary Vascular Damage Induced by Bone Marrow Transplantation

Concerning the effects of BMT on pulmonary circulation, it has been known since 1984 a link between BMT and the development of PVOD, thus providing the earliest evidence that bone marrow compartment could adversely affect the pulmonary vasculature [17]. The incidence of PAH in post-childhood cancer therapy and BMT is estimated to be 1.6% based on single-center experience [1]. From a pathophysiological standpoint, it has been shown that bone marrow-derived cells contribute to the pathogenesis of pulmonary arterial hypertension inducing remodeling and inflammation [18]. Endothelial cell injury has been shown after allogenic BMT and has been directly linked to the development of several implications including graft-versus-host disease, PVOD, and endothelial leakage syndrome. Endothelial alterations could occur also in the pulmonary circulation, determining an imbalance in pulmonary vascular mediators, thus causing pulmonary vasoconstriction and remodeling of the vascular structure [1]. Currently, deeper knowledge of the actual mechanisms that underlie the development of BMT-related PH is not available.

Mechanisms of Pulmonary Vascular Damage Induced by Mitomycin C and Bleomycin

Mitomycin C can induce PVOD. This condition is an uncommon form of PH typically characterized by the obstruction of small pulmonary veins and a poor prognosis. Patients with PVOD typically present with precapillary PH, peculiar thoracic high-resolution CT alterations, a low diffusing capacity of the lung for carbon monoxide, and severe hypoxemia. The estimated incidence of PVOD in patients treated with mitomycin is 3.9 per 1000 per year, which is relevantly higher in comparison to its incidence in the general population (0.5/million per year) [11]. Furthermore, females seemed to be more susceptible to mitomycin toxicity.

Several mechanisms have been described to concur in the development of mitomycin-induced PVOD. This drug is an alkylating agent commonly used in several regimens for the treatment of different cancers [19]. The main mechanism of action of this drug implies its covalent binding to DNA determining DNA synthesis inhibition [20]. It results in decrease in cell viability and induces apoptosis in corneal endothelial cells [21]. Recent studies further demonstrated that mitomycin inhibits vascular endothelial growth factor (VEGF) expression [22], causing apoptosis resistance and unlimited endothelial cell proliferation, similar to what happens in the sugen/hypoxic rat model [22]. In rats, intraperitoneal administration of mitomycin caused major remodeling of small pulmonary veins associated with foci of intense microvascular endothelial cell proliferation consistent with PVOD [11]. These alterations were prevented by the administration of amifostine, a cytoprotective adjuvant used in chemotherapeutic and radiotherapeutic regimens involving DNA-binding chemotherapeutic agents [11].

Bleomycin, another chemotherapeutic drug belonging to the class of the antibiotics and commonly used for the treatment of lymphomas, is also associated with the occurrence of PH [23]. The overall risk of pulmonary toxicity is about 10%. Pulmonary hypertension due to bleomycin is secondary to the development of pulmonary fibrosis. The underlying mechanism is mainly related to oxidative damage, relative deficiency of the deactivating enzyme bleomycin hydrolase, genetic susceptibility, and production of inflammatory cytokines [24].

Mechanisms of Pulmonary Vascular Damage Induced by Alkylating Agents

Alkylating agents may be responsible of the development of PVOD rather than PAH, and this form of toxicity has been known for several years [12].

Cyclophosphamide, an alkylating agent, is used as immunosuppressant in several autoimmune diseases and as a common component of multidrug regimens for treatment of hematological and solid cancers. In different animal models, cyclophosphamide demonstrated to be able to induce PH. From a histopathological standpoint, all these models revealed significant alterations of the pulmonary venules and veins, highly suggestive of PVOD [2]. Specifically, cyclophosphamide induced pulmonary vein wall thickening due to adventitial and transmural inflammatory infiltration and fibrosis, muscularization of distal microvessels with foci of pulmonary congestion, consistent with PVOD [2]. It has been demonstrated that endothelial cells are more susceptible to the effector of cyclophosphamide than other cell types [25, 26].

Mechanisms of Pulmonary Vascular Damage Induced by Dasatinib

The actual incidence of PAH during treatment with dasatinib is still a matter of debate, ranging from 0.6% up to 11% [3].

From a clinical standpoint, median delay for dasatinib-induced PAH diagnosis is usually 34 months (ranging from 8 to 40 months after exposure to the drug). Unlike other forms of PAH, dasatinib-induced PAH is often reversible after drug discontinuation or replacement with another TKI, such as nilotinib [3, 27–30]. In some cases, because of the persistence of

symptoms and of the increase in pulmonary arterial pressures, specific treatment with pulmonary vasodilator agents has been prescribed, with beneficial results [3, 27–30].

Dasatinib, as already mentioned above, is an oral second-generation TKI recently approved as a first- or second-line treatment for chronic Philadelphia chromosome-positive (which corresponds to the reciprocal translocation between chromosome 9 and 22, thus causing the Abelson TK gene, ABL, to fuse with the breakpoint cluster region of the BRC gene) myelogenous leukemia [31, 32] and currently approved also for second-line treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia [33]. The BCR/ABL oncogene is responsible for a pathogenic tyrosine kinase signal transduction protein that triggers intracellular signaling, activating multiple transduction cascades. This pathway promotes growth, proliferation, and survival of hematopoietic cells [34] and plays a role in defective DNA repair, alteration of cellular adhesion, and inhibition of apoptosis [35]. Deregulated BCR/ABL tyrosine kinase activity is the molecular marker for chronic myelogenous leukemia. Drugs like imatinib, nilotinib, and dasatinib that target BCR/ABL tyrosine kinase and block its activity lead to the induction of apoptosis and inhibits malignant cells' proliferation [36]. Dasatinib, characterized by a 300-fold higher affinity for BRC/ABL kinase in comparison with imatinib, is more effective in patients who failed treatment with imatinib [37]. However, dasatinib is also able to inhibit several other kinases, including the Src, a family of receptors that play a crucial role in smooth muscle cell proliferation and vasoconstriction. Therefore, is has been hypothesized that this drug could alter the proliferation/antiproliferation balance in endothelial and pulmonary arterial smooth muscle cells, thus determining adverse remodeling of pulmonary arterioles and then PAH [38, 39].

Several receptor tyrosine kinases, such as platelet-derived growth factor (PDGF) receptor beta and VEGF receptor 2, are implicated in the pathophysiology of PAH. In particular, PDGF signaling pathway mediates endothelial cell dysfunction and proliferation and migration of vascular smooth muscular cells [40–42]. It has been demonstrated that, beside perturbation of the balance between vasoconstriction and vasodilation, PDGF ligands and receptors are increased in idiopathic PAH. In addition, PDGF was shown to primarily contribute in vascular smooth muscle cell proliferation and hyperplasia in PAH [43, 44]. Interestingly, another TKI inhibitor, imatinib, has been shown to have anti-vasoproliferative properties and to be effective in improving hemodynamics in both animal models and in a randomized controlled clinical trial [44, 45]. Nevertheless, the use of imatinib for treatment of PAH has been discouraged because of severe adverse events, relevant side effects, and high discontinuation rate during the open-label extension phase study [46].

Mechanistically, imatinib reversed the overexpression and increased phosphorylation of PDGF receptor beta that is present also in pulmonary arteries from animal models of PH, inhibited PDGF receptor-related ERK1/2 activation in lungs of these animals thereby suppressing pulmonary artery smooth muscle cell proliferation and inducing cellular apoptosis [44]. While significantly lower concentrations of dasatinib are needed to obtain BCR/ABL inhibition in comparison to imatinib, the effect of dasatinib on c-kit and PDGF receptor are rather similar. In addition, and differently from imatinib, dasatinib also inhibits the SRC family of kinases [47]. The large spectrum of inhibition of dasatinib led to hypothesize that by inhibiting Src, a family of receptors that play a crucial role in smooth muscle cell proliferation and vasoconstriction, this drug could alter the proliferation/antiproliferation balance in endothelial and pulmonary arterial smooth muscle cells besides its inhibition of PDGF receptor (that instead determines an improvement of pulmonary vascular disease) [38]. Whether this aspect of the compound is causally related to PAH development is still poorly understood.

The extreme differences in terms of effects on pulmonary circulation between imatinib and dasatinib suggest that dasatinib-induced pulmonary vascular toxicity is molecule-related rather than class-related. On the other side, in vivo and

in vitro studies aimed at evaluating the effects of dasatinib and imatinib on pulmonary vasculature demonstrated that both TKI increased levels of nitric oxide, a potent vasodilator, without inducing PAH-related adverse remodeling, thus suggesting that both the drugs could promote beneficial effects for PAH [48]. These results are in contrast with the clinical evidence of dasatinib-induced PAH. In conclusion, there is still poor knowledge about the actual mechanisms underlying the damage of pulmonary vessels induced by dasatinib.

Screening and Clinical Management of Anticancer Drug-Induced Pulmonary Hypertension

Before initiation of antineoplastic drugs that have a known possible risk of causing PAH, baseline evaluation for signs and symptoms of underlying cardiopulmonary disease is mandatory. Echocardiographic assessment, including the search for signs of right ventricular overload, should be considered [49]. Transthoracic echocardiography is used to explore the effects of increase in pulmonary pressure on the heart, especially on the right ventricle, and to estimate pulmonary arterial systolic pressure from continuous wave Doppler measurements of the tricuspid regurgitation [50]. This evaluation before chemotherapy initiation may help in interpretation of follow-up echocardiographic examinations in patients reporting symptoms potentially correlated with the development of PAH, like exercise limitation or exertional dyspnea during treatment. Noninvasive cardiovascular surveillance should be considered in all patients during treatment with cancer drugs known to cause PAH or pulmonary vascular damage, particularly in case of the appearance of new symptoms like exertional dyspnea, fatigue, or angina.

The recently published position paper of the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology suggests to consider echocardiographic evaluation every 3 to 6 months in asymptomatic patients. It is unclear whether patients with baseline signs of right ventricular overload due to comorbidities commonly associated with elevated pulmonary arterial pressure (e.g., chronic obstructive pulmonary disease, left heart dysfunction) are at higher risk of chemotherapy-induced PAH and require more frequent surveillance with echocardiography. When drug-induced PAH is suspected, referral to a specialized pulmonary hypertension team is recommended to assess indications for right heart catheterization [4]. Multidisciplinary team discussions should be held among Cardiologists, Oncologists and Hematologists regarding the risk–benefit ratio of continuing cancer treatment with PAH drug therapy vs. stopping or replacing the culprit drug [4]. Chemotherapy-induced PAH is often reversible with drug cessation (e.g., in the case of dasatinib), although usually without restoration of normal right heart hemodynamics [3]. Targeted therapy for PAH may be useful temporarily or permanently.

Remarks and Conclusion

PH remains a rare complication of antineoplastic drugs, suggesting possible individual susceptibility, and further studies are needed to better understand the underlying mechanisms, to identify patients at risk of developing pulmonary vascular toxicity and how to manage and treat this condition.

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Venous Thromboembolism

15

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Background

Venous thromboembolism (VTE) is particularly common in cancer patients. Among all patients with VTE, 20% have underlying active malignancy [1]. VTE may be the presenting sign of an occult malignancy, and 10% of patients with idiopathic VTE develop cancer within 2 years [2]. Among hospitalized cancer patients, the cumulative incidence of deep venous thrombosis (DVT) has been reported at 4.6% [3]. On the other hand, up to 50% of cancer patients were found to have evidence of DVT at autopsy [4]. Compared to controls, patients with cancer have a higher risk of first and recurrent VTE, as well as bleeding on anticoagulants.

The heterogeneity of the studies makes it difficult to accurately compare rates of venous thrombosis between these studies, and the large variations in the reported incidence and absolute risk are likely related to variation in patient population, duration of follow-up, and the patient's characteristics. Cancer patients' risks for developing DVT vary among cancer patients and depend on multiple clinical variables including tumor type, the stage or extent of the cancer, age, immobilization, other medical comorbidities, and treatment with surgery or certain chemotherapeutic agents. The pathophysiology of the prothrombotic state in cancer patients is in fact complex and multifactorial, including the acquired hypercoagulable state related to tumor-activated tissue factors, cancer procoagulants, carcinoma mucins, and inflammatory cytokines, combined with venous stasis and vascular dysfunction related to endothelial injury provoked by toxicity of chemotherapy and biologic drugs, radiation, and central venous catheters (Fig. 15.1) [5].

Cancer-associated thromboembolism is a source of significant morbidity and mortality. These events often require long-term anticoagulation with associated increase in bleeding and recurrence rates. Thromboembolism has also been shown to be a leading cause of death in cancer patients undergoing active chemotherapy [6]. These patients have a worse prognosis than patients with cancer who did not have venous thromboembolism, and survival is particularly poor when the diagnosis of cancer is concurrent with the thromboembolic event [7].

Mechanism

Patients with underlying malignancy or hematologic disorders have added risk for in situ thrombosis related to the inherent thrombophilia

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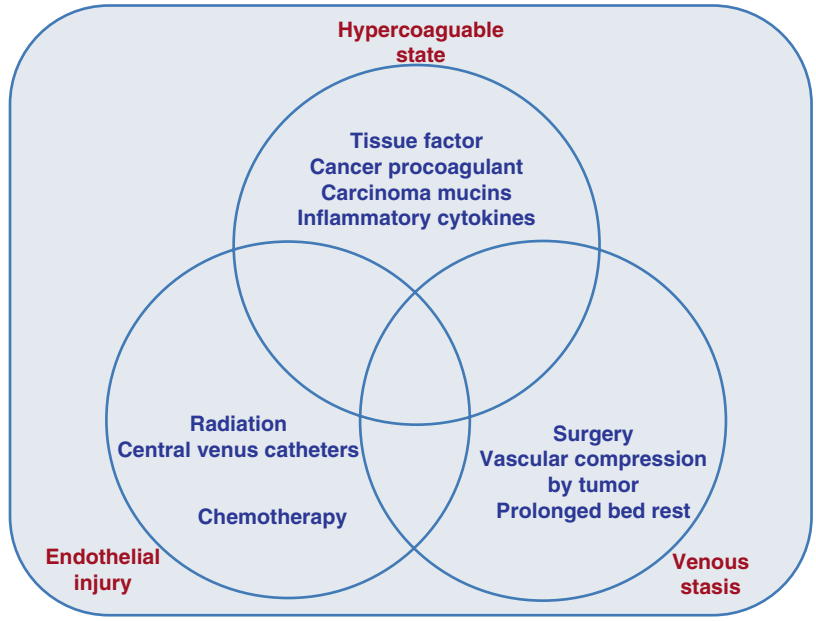

Fig. 15.1 Mechanisms of cancer-associated VTE

associated with their malignancy and its therapy. Multifactorial and complex mechanistic etiologies have been implicated in the pathogenesis of thrombosis in the setting of underlying cancer; this includes local and systemic activation of the coagulation cascade, thrombocytosis, factor C and S depletion, increased fibrinogen levels, and inhibition of fibrinolysis. On the other hand, endothelial damage triggered by cancer cell-mediated vessel injury or an iatrogenic mechanism (vessel catheterization, surgery, and chemotherapeutic agents) has also been suggested as a potential cause leading to excessive thrombosis [8, 9].

A key step leading to excessive thrombosis is the ability of tumor cells to produce and release several procoagulant substances such as tissue factor and cancer procoagulant, which activates platelets, factor X, and the clotting cascade. In addition, anticancer therapy (i.e., surgery/chemotherapy/hormone therapy) may significantly increase the risk of thromboembolic events by similar mechanisms including procoagulant release, endothelial damage, or stimulation of tissue factor production by host cells [10, 11].

Chemotherapeutic agents are now identified as an independent risk factor for thrombosis in cancer patients. In general, mechanisms for these events have included chemotherapy-induced expression of macrophage-monocyte tissue factor, endogenous procoagulant-anticoagulant mismatch, accentuated tumor and endothelial cell death, cytokine release resulting in increased expression of tissue factor, and enhanced endothelial cell reactivity to platelets [12, 13].

Regarding cancer drugs, each new cancer drug will have its own typical way of acting with an unpredictable risk of toxicity, and the risk of venous thromboembolic events is higher in the first 30-day period of chemotherapy [14–16].

Table 15.1 shows the family of cancer drugs most often associated with VTE. For example, angiogenesis inhibitors are associated with a considerable risk of VTE [17, 18].

Management

Cancer patients often face the challenge of having multiple comorbidities which can impact the choice and the dosing of pharmacologic anticoagulants. This includes, for example, the complexity related to an inherent hypercoagulable state, the higher than usual bleeding risk during thrombocytopenia, and the complexity of drug-drug interactions between anticoagulants and several chemotherapies. Indications for VTE

Table 15.1 Cancer therapy associated with venous thromboembolism

Chemotherapy agents
Small molecule tyrosine kinase inhibitors
Trametinib
Sunitinib
Dabrafenib
Erlotinib
Cabozantinib
Pazopanib
Axitinib
Monoclonal antibody-based tyrosine kinase inhibitor
Bevacizumab
Angiogenesis inhibitors
Lenalidomide
Thalidomide
Pomalidomide
Histone deacetylase inhibitor
Vorinostat
Alkylating agent
Cisplatin

Table 15.2 Khorana score

Patient characteristics	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350,000 / mm^3	1
Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count >11,000 / mm^3	1
Body mass index ≥35 kg/m^2 or more	1

Modified from Khorana et al. [21]
High-risk score ≥3
Intermediate-risk score 1–2
Low-risk score 0

prophylaxis and treatment of acute VTE events in these patients are aimed at decreasing DVT occurrence, preventing extension into pulmonary embolism, and minimizing VTE recurrence. The patient clinical and location setting, the duration of therapy, and the choice of the pharmacologic approach for such therapy sometimes differ from those of patients without underlying cancer.

DVT Prophylaxis

The use of anticoagulation for prophylaxis against VTE in patients with cancer is different between the ambulatory and the inpatient settings. While the vast majority of hospitalized cancer patients receive a certain form of anticoagulation for DVT prophylaxis, studies have shown the limited benefit of such approach in the ambulatory setting except in those receiving high-risk medications and specifically multiple myeloma patients being treated with a combination of immunomodulatory therapy and steroids. In fact, patients receiving lenalidomide or thalidomide in combination with dexamethasone are at a significantly higher risk for VTE and are usually treated with prophylactic dose of aspirin or warfarin or low-molecular-weight heparin based on their risk profile [19].

The role of the newest direct oral anticoagulants (DOACs) in the prevention of VTE in high-risk ambulatory cancer patients is currently under investigation. These high-risk ambulatory patients can be identified using a risk stratification model for VTE according to Khorana [20, 21] (Table 15.2).

There are several ongoing studies with DOACs in this field. Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients: A Randomized Placebo-Controlled, Double-Blind Clinical Trial (NCT02048865) and A Phase 2 Pilot Study of Apixaban for the Prevention of Thromboembolic Events in Patients with Advanced (Metastatic) Cancer (NCT00320255) are ongoing studies that aim to understand whether apixaban therapy is well-tolerated in cancer patients and acceptable as anticoagulant therapy when administered to patients with advanced or metastatic cancer and at increased risk for venous thromboembolic events.

Other studies oriented on a particular kind of cancer are oral apixaban versus enoxaparin for thromboprophylaxis in women with suspected pelvic malignancy (NCT02366871) and evaluation of the use of apixaban in prevention of thromboembolism disease in patients with myeloma (NCT02958969).

Other authors are testing rivaroxaban in this field: "Efficacy and safety of rivaroxaban pro-

phylaxis compared with placebo in ambulatory cancer patients initiating systemic cancer therapy and at high risk for venous thromboembolism" (NCT02555878) is designed to demonstrate that rivaroxaban is superior to placebo in reducing the risk of DVT and pulmonary embolism [22].

Treatment Options for VTE in Cancer Patients

The armamentarium of anticoagulation therapy for DVT in the general population includes warfarin, low-molecular-weight heparin (LMWH), fondaparinux, and DOACs. In patients with malignancy, LMWH is the long-term anticoagulant of choice for the management of VTE based on its safety and efficacy and also its superiority in reducing VTE recurrence rate compared to other agents. Warfarin and fondaparinux are both associated with similar bleeding risks as LMWH, but both are associated with a higher recurrence rate [23, 24]. Other advantages of LMWH compared to warfarin include the more predictable response and standardized dosing with less drug-drug interaction.

Instead, for the newer oral anticoagulation agents, some expert panels, such as the National Comprehensive Cancer Network (NCCN) guidelines, recommend against the use of these drugs in patients with cancer based on the limited data regarding their safety in patients with active malignancy [25]. Even though, as we have already said, in patients with VTE and cancer, the latest guidelines (Chest 2016) continue to recommend the use of LMWH over VKAs or DOACs, but for patients not treated with LMWH they suggest the indiscriminate use of DOACs or VKAs [18].

Limited clinical data suggest a similar efficacy between DOACs and warfarin in cancer patients with VTE. The scarce safety and effectiveness outcome data in cancer patients were derived mainly from limited observational studies and from several small subgroup analysis studies obtained from large clinical trials that mainly included noncancer patients [26–28] and typically excluded patients undergoing active chemotherapy. These studies have the usual inherent limitations of meta-analyses related to the difference and the heterogeneity of trial protocols like baseline patients' clinical characteristics and the predefined outcomes and complications. Moreover, there are several clinical and metabolic features in cancer patients that can alter the DOAC pharmacodynamics with a secondary unpredictable clinical response to these drugs. These features include altered renal and hepatic functions, cancer cachexia and malnutrition, coagulopathy, and thrombocytopenia and, more importantly, the unpredicted response caused by drug-drug interaction with cancer therapies. In fact, data about the combined use of chemotherapeutic agents and DOACs are rare. DOACs may interact with CYP3A4 and P-glycoprotein, making them theoretically susceptible to plasma concentrations' fluctuations when taken with inhibitors or inducers of these enzymes. Several categories of chemotherapeutic agents, including antimitotic microtubule inhibitors, tyrosine kinase inhibitors, and immune-modulating agents, are known substrates to either or both of CYP3A4 and P-glycoprotein [29, 30]. Theoretically, these types of pharmacodynamic drug-drug interactions can lead to attenuation of the DOAC effects, increasing the risk of thrombosis, or exacerbation of their anticoagulation effects leading to an increase in bleeding risks.

The current NCCN guidelines recommend against the use of DOACs in patients with active cancer [25]. These recommendations are based mainly on the many reasons listed above and will likely hold until more safety data are available. There are currently multiple randomized and also observational ongoing trials investigating the safety and efficacy of these drugs in cancer patients that will hopefully further clarify the role of these drugs in managing cancer patients [31]. The following is an overview of the available literature in this regard.

The CLOT study in 2003 demonstrated that in patients with cancer and acute VTE, dalteparin was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding [23]. This study evaluated the efficacy of LMWH dalteparin versus warfarin in the secondary prevention of thrombosis in cancer patients. After a first VTE event, patients were randomized to receive standard treatment with LMWH (dalteparin for 5–7 days plus the oral anticoagulant for 6 months) or dalteparin for 1 month, followed by a dose equivalent to 70–80% of the initial for the following 5 months. Treatment with LMWH for 6 months has reduced recurrence of thromboembolic events from 17% to 9% ($p = 0.0017$), compared to treatment with dicumarols, without increasing major bleeding [23].

The efficacy and safety of LMWH were again demonstrated by another study conducted by Lee et al. [32]. These authors (CATCH investigators) evaluated patients with acute VTE who were randomized to receive 3 months of warfarin at INR between two and three for enoxaparin. The study evaluated a combined outcome of major bleeding and thrombotic recurrence. In the warfarin group, the outcome was 21% versus 10.5% of the enoxaparin group. This difference was particularly due to the difference in the major bleeding events.

According to the data provided by these studies, LMWH has been considered the standard therapy in the secondary prophylaxis of cancer-related VTE. The therapy with warfarin, in fact, is particularly complicated in cancer patients for several reasons: it is often very difficult to maintain the INR within the correct range as patients with cancer often suffer from vomiting and loss of appetite or may have forced diet or alteration of intestinal absorption and/or liver function [33]. Moreover, pharmacological interactions of concomitant therapies may widely interfere with the vitamin K-dependent drugs. Finally, another limiting factor is due to the discontinuation of anticoagulant therapy for the need of microinvasive procedures (thoracentesis, biopsies, or others) or elapsing thrombocytopenia [33].

Different were the conclusions of CATCH investigators [32]. Among patients with active cancer and acute symptomatic VTE, the use of full-dose tinzaparin (175 IU/Kg) daily compared with warfarin for 6 months did not significantly reduce recurrence of VTE and was not associated with reductions in overall mortality or major bleeding but was associated with a lower rate of clinically relevant non-major bleeding. This difference could be due to the chemotherapeutic agents/regimens that have become much more advanced over the past decade and to the fact that the CATCH patients were less sick, with less metastatic disease, than the CLOT cohort [23].

After these studies on LMWH, important trials about DOACs and VTE were published. These papers were followed by several subgroup analyses on cancer patients. In the "Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE randomized studies," the authors concluded that in patients with active cancer and VTE, rivaroxaban has similar efficacy to prevent recurrence of VTE and reduces the number of major bleeding events compared with treatment with enoxaparin and VKA, although there was no difference between groups for clinically relevant bleeding [34]. In the "Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer" study, data from two randomized trials (RECOVER AND RECOVER II) were pooled to evaluate the efficacy and safety of dabigatran compared to warfarin. The study concluded that in cancer patients, dabigatran provided similar clinical benefit as warfarin [35]. In the AMPLIFY study, 5,395 patients with acute VTE were enrolled to compare apixaban with enoxaparin followed by warfarin, concluding that apixaban was not inferior to warfarin, also in the treatment of patients with VTE and cancer [36].

Three meta-analyses, recently published, have reported a similar efficacy and safety of DOACs in cancer patients with respect to the general population. The meta-analysis published

by Van Der Hulle et al., which includes five studies for a total of 19,060 patients, indicates that the efficacy and safety of DOACS are at least comparable to those of AVK [37]. The meta-analysis published by Vedovati et al., which considers six studies including 1,132 patients, indicates that DOACS give similar incidences of recurrent VTE and major bleeding compared to conventional therapy (heparin plus warfarin) [26].

The network meta-analysis published by Posch et al., which includes 10 randomized controlled trials for a total of 3,242 cancer patients suffering from acute VTE, indicates that LMWH and DOACS can be comparable with respect to prevention of recurrent VTE and risk of major bleeding [38].

Following these studies and meta-analyses, the latest guidelines, published in *Chest* 2016, have significantly modified the approach to anticoagulation in VTE, so in patients with VTE and cancer, the use of LMWH compared with VKAs or DOACs is still recommended; but for those who are not treated with LMWH, there are no more preferences between DOACs and VKAs [18]. This is a significant change from the previous guidelines published in *Chest* 2012, in which, in patients with VTE or pulmonary embolism (PE) and cancer that were not treated with LMWH, the use of VKAs was recommended compared to dabigatran and rivaroxaban (the only available DOACs at the time).

After the guidelines published in *Chest* 2016, an important work on the same topic was published by Raskob et al. [39]. A subgroup analysis was performed on 771 patients with any history of cancer enrolled in the Hokusai-VTE trial; 378 of the 771 patients were assigned to heparin-edoxaban and 393 to heparin-warfarin treatment. Among the 378 cancer patients in the edoxaban group, the incidence of VTE recurrence was 4% (14 patients), while the incidence of clinically relevant bleeding (major or non-major) was 12% (47 patients) [40]. Among the 393 cancer patients in the warfarin group, the incidence of VTE recurrence was 7% (28 patients), while the incidence of clinically relevant bleeding (major or non-major) was 19% (74 patients). The results of this study suggest that in cancer patients, edoxaban is as effective as warfarin for preventing recurrent VTE and major bleeding. Moreover, a significant reduction in clinically relevant non-major bleeding has been found in the edoxaban group. Anyway, further studies were required to compare DOACs directly with LMWH that is the recommended anticoagulant of choice in cancer patients.

To this end, the results of Hokusai-VTE Cancer trial have been recently published (Fig. 15.2). This study has demonstrated that oral edoxaban was non-inferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was numerically, but not significantly, lower, and the rate of major bleeding

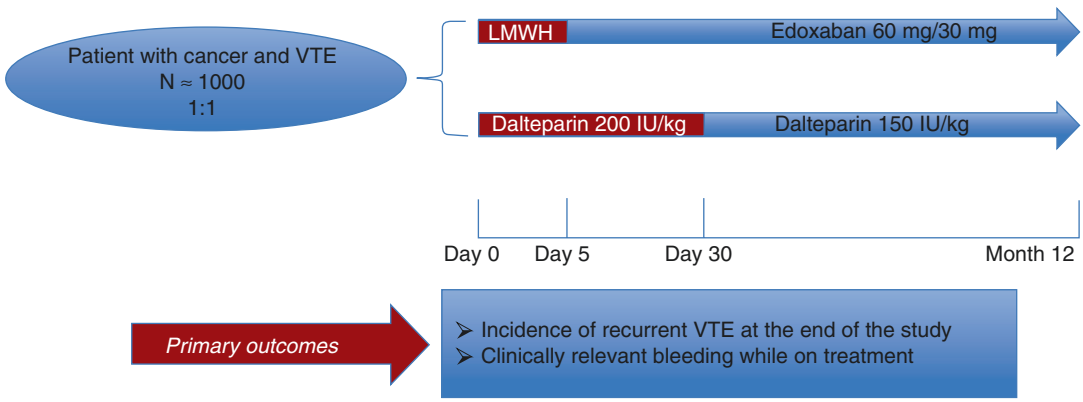

Fig. 15.2 Hokusai-VTE Cancer study

was significantly higher with edoxaban than with dalteparin, but the frequency of severe major bleeding (category 3 or 4) was similar. In a next subgroup analysis, if we exclude gastrointestinal cancer, and precisely upper gastrointestinal, there was no more difference in major bleeding between edoxaban and dalteparin [41].

In the "Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism: Results of the Select-D Pilot Trial" presented at the American Society of Hematology Meeting 2017, the treatment with rivaroxaban resulted in a very low VTE recurrence rate at 6 months with a similar number of major bleedings reported across trial arms, but more clinically relevant non-major bleeds were seen with rivaroxaban.

Also the CARAVAGGIO study "Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer", starting in these months, is designed to evaluate whether apixaban is not inferior to dalteparin, in terms of efficacy and safety, in the treatment of VTE in cancer patients [NCT03045406].

Treatment

In any event, until a better understanding of bleeding risks related to DOACs' pharmacodynamic interaction with chemotherapy and better evidence of clinical safety are both available, vigilance and caution are recommended when using DOACs in cancer patients, in particular when combined with drugs that strongly interact with CYP3A4 or P-glycoprotein (Tables 15.3 and 15.4). Table 15.5 shows a suggested reasonable approach at selecting cancer patients for DOACs when they are receiving concomitant cancer therapies [42–45].

Table 15.3 Cancer drug interactions with P-glycoprotein

Substrate	Inducer	Inhibitor
Vinblastine, vincristine, docetaxel, paclitaxel, methotrexate, irinotecan, etoposide, doxorubicin, daunorubicin, idarubicin, bendamustine, mitomycin C, imatinib, nilotinib, lapatinib, crizotinib, vemurafenib, cyclosporine, sirolimus, everolimus, temsirolimus, tacrolimus, dexamethasone, lenalidomide, ondansetron	Vinblastine, doxorubicin, dexamethasone	Imatinib, nilotinib, lapatinib, sunitinib, crizotinib, vandetanib, tamoxifen, enzalutamide, abiraterone, cyclosporine, dexamethasone, tacrolimus

Table 15.4 Cancer drug interactions with cytochrome P450 3A4

Substrate	Inducer	Inhibitor
Vinblastine, vincristine, vinorelbine, docetaxel, paclitaxel, irinotecano, etoposide, doxorubicin, cyclophosphamide, ifosfamide, busulfan, imatinib, dasatinib, nilotinib, erlotinib, gefitinib, lapatinib, sunitinib, sorafenib, crizotinib, vemurafenib, vandetanib, brentuximab, tamoxifen, letrozole, fulvestrant, flutamide, enzalutamide, abiraterone, cyclosporine, sirolimus, everolimus, temsirolimus, tacrolimus, dexamethasone, prednisone, bortezomib, bexarotene, ondansetron, palonosetron, aprepitant, fosaprepitant, oxycodone, fentanyl, methadone, acetaminophen, clonazepam	Paclitaxel, vemurafenib, enzalutamide, dexamethasone, prednisone, bexarotene, aprepitant, fosaprepitant	Vinblastine, vincristine, vinorelbine, docetaxel, etoposide, doxorubicin, idarubicin, cyclophosphamide, ifosfamide, lomustine, imatinib, dasatinib, nilotinib, lapatinib, crizotinib, tamoxifen, anastrozole, bicalutamide, abiraterone, cyclosporine, sirolimus, temsirolimus, tacrolimus, bortezomib, aprepitant, fosaprepitant, fentanyl, methadone, acetaminophen

Table 15.5 Criteria for DOAC use in cancer patients requiring anticoagulation

Patient assessment
Risk factors for bleeding
No major bleeding events in the past 2 months
Absence of intracranial or visceral tumor at high risk for major bleeding
Platelets
Platelet count >50,000 per mL
No anticipated decrease due to disease or chemotherapy
Coagulation studies
Normal PT, PTT, and fibrinogen
Liver function tests
No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function
CrCl >30 mL/min
No anticipated fluctuations due to nephrotoxic chemotherapy
Medications
No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein (antifungals, immunosuppressive, antiepileptic, etc.)
Consider the lists of chemotherapeutic, biological, hormonal, or support drugs that modulate the cytochrome P450 3A4 and/or P-glycoprotein
Good medication compliance

Modified from Short and Connors [42]

Conclusions

LMWHs are at the moment regarded as the basis of VTE treatment and prevention in cancer patients as per the American Society of Clinical Oncology latest guideline update. There are currently several trials assessing the role of DOACs in preventing and treating VTE in patients with underlying malignancy, one already published: the Hokusai-VTE cancer trial. Until a better understanding of bleeding risks related to DOACs' pharmacodynamics interaction with chemotherapy and better evidence of clinical safety are both available, we recommend vigilance and caution when using DOACs in cancer patients. This is particularly the case when a pathological pericardial process is suspected or if DOACs were to be combined with drugs that strongly interact with CYP3A4 or P-glycoprotein. We also recommend caution against their use with chemotherapy drugs that are known to be associated with platelet dysfunction or increased bleeding risks. This is especially important since well-established alternative therapies, specifically low-molecular-weight heparin, have been proven to be effective and safe.

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Early Detection of Cardiac Damage

16

Giuseppina Novo, Cinzia Nugara, and Patrizio Lancellotti

Introduction

Advances in the early diagnosis, staging, and therapy have significantly reduced the mortality and increased longevity in cancer patients. An estimated 14.5 million people are currently living with a history of cancer in the USA. This number is projected to rise to 19 million over the next 10 years [1]. A significant proportion of cancer survivors are living with long-term adverse effects of cancer therapy, involving multiple organ systems. Cardiovascular toxicity of cancer therapy is a major concern in this regard.

Cancer therapies, especially anthracyclines and monoclonal antibodies, have been linked with increased rates of cardiotoxicity (CTX). The clinical manifestations of cardiotoxicity are broad and can include heart failure, cardiomyopathies, arrhythmias, ischaemia, valves heart disease, pericardial disease, hypertension, or thrombosis. Cancer therapeutics-related cardiac dysfunction (CTRCD) is reported in 2–3% in randomized trials on breast cancer women treated with anthracyclines and trastuzumab but can reach up to 26% in observational studies [2].

It is clear that symptom-based monitoring is ineffective because when they occur, damage is already advanced, and therefore it is recommended after a baseline evaluation to monitor cardiac function to promptly detect any variation. Early detection and quantification of cardiac damage is required to readily intervene with cardioprotective therapy and to allow the prosecution of antineoplastic treatment and avoid the need of its discontinuation. Therefore, cardio-oncology is a newly emerging subspecialty of cardiology with the aim of monitoring, early diagnosis, prevention, and treatment of cardiotoxicity related to cancer therapies and careful planning of chemotherapy in patients with pre-existing cardiovascular disease to avoid overt cardiotoxicity and heart failure.

Many strategies are available to monitor cardiac function during or after chemotherapy including cardiac imaging (echocardiography, nuclear imaging, cardiac magnetic resonance) and biomarkers (troponin, natriuretic peptides).

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Table 16.1 Diagnostic tools for the detection of cardiotoxicity

Technique	Diagnostic criteria	Advantages	Major limitations
Echocardiography: – 3D-based LVEF – 2D Simpson's LVEF – GLS	• LVEF: >10 percentage points decrease to a value below the LLN suggests CTX • GLS: >15% relative percentage reduction from baseline may suggest risk of CTX	• Wide availability • Lack of radiation • Assessment of haemodynamics and other cardiac structures	• Inter-observer variability • Image quality • GLS: inter-vendor variability, technical requirements
Nuclear cardiac imaging	• >10 percentage points decrease in patients with CTX	• Reproducibility	• Cumulative radiation exposure • Limited structural/ functional information on other cardiac structures
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderline	• Accuracy, reproducibility • Detection of diffuse myocardial fibrosis using T1/T2 mapping	• Limited availability • Patient's adaptation (claustrophobia, breath hold, long acquisition times)
Cardiac biomarkers: – TnI – hsTnI – BNP – NT-proBNP	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation	• Accuracy, reproducibility • Wide availability • High sensitivity	• Insufficient evidence to establish the significance of subtle rises • Variations with different assays • Role for routine surveillance not clearly established

Adapted from Zamorano et al. [3]
BNP B-type natriuretic peptide, *CTX* cardiotoxicity, *GLS* global longitudinal strain, *hsTnI* high-sensitivity troponin I, *LLN* lower limit of normality, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal fragment B-type natriuretic peptide, *TnI* troponin I

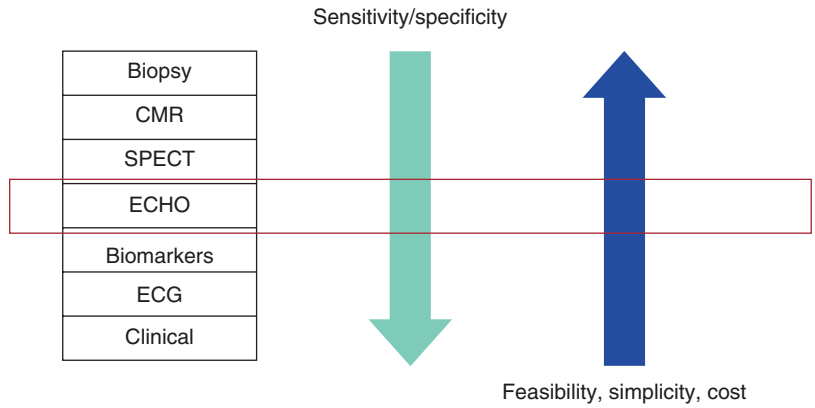

Fig. 16.1 Echocardiography vs. other modalities for detection of cancer therapeutics-related cardiac dysfunction. (Adapted from Zito et al. [4])

The choice of different modalities depends upon local expertise and availability [3]. Table 16.1 summarizes the main techniques available and current diagnostic criteria.

Echocardiography

Monitoring with 2D echocardiography is the most frequently used technique in clinical practice because of its safety, wide availability, repeatability, and low cost (Fig. 16.1). Echocardiographic technology has been continuously evolving, with two major developments being real-time three-dimensional echocardiography (3DE) and myocardial deformation imaging.

For conventional analysis, left ventricular volumes and left ventricular ejection fraction (LVEF) are the most widely used parameters to detect CTX [5, 6]. The method for 2D echocar-

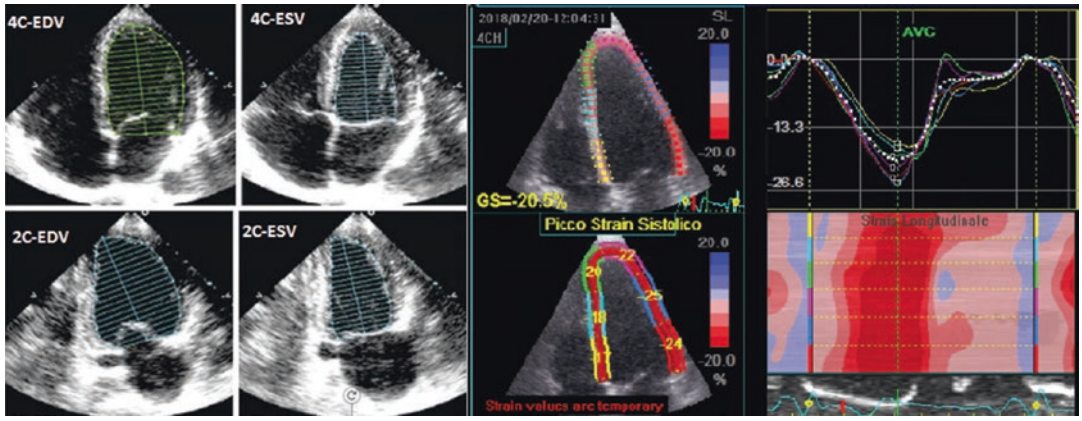

Fig. 16.2 Left panel: Simpson's biplane method. Right panel: speckle-tracking echocardiography (STE)

diographic volume calculations recommended by the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) is the biplane method of disc summation (modified Simpson's rule). Volume measurements are based on tracings of the blood tissue interface in the apical four- and two-chamber views. At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line. Left ventricle (LV) length is defined as the distance between the middle of this line and the most distant point of the LV contour (Fig. 16.2, left panel). The LVEF is then calculated using the following formula: LVEF = (LVEDV − LVESV)/LVEDV; (LVED LV end-diastolic volume, LVESV LV end-systolic volume). Normal LVEF using biplane method of discs is 63% ± 5%, and LVEF in the range of 53–73% is classified as normal [7].

CRTCD is defined as a 10% decrease of left ventricle ejection fraction to a value below the normal limit of normal confirmed in repeated studies (at 2–3 weeks).

Newer echocardiography techniques, using contrast echocardiography or 3D technology, have resulted in significant improvement in the accuracy of LVEF assessment. Contrast agents should be used to improve endocardial delineation when two or more contiguous left ventricle endocardial segments are poorly visualized in apical views [7, 8]. Contrast-enhanced images may provide larger volumes than unenhanced images that are closer to those obtained with cardiac magnetic resonance (CMR) [9].

In patients with good image quality, 3D echocardiographic measurements are accurate and reproducible and should therefore be used if available [7]. One of the advantages of 3D echocardiographic volume measurements is that they do not rely on geometric assumptions.

A small study of 50 patients with breast cancer undergoing serial LVEF assessments demonstrated that 3D echocardiography was feasible and reproducible for assessing changes in LV volumes and LVEF compared with the gold standard cardiac MRI [10]. Thavendiranathan et al. showed that non-contrast 3D echocardiography was the most reproducible technique for LVEF assessment, capable of detecting smaller changes in LVEF (~5%) [11].

Unfortunately, impairment of LVEF is detectable only after that a considerable cell loss has taken place [12, 13] and thus too late to allow effective prevention. For this reason, new markers of systolic dysfunction have been investigated to earlier detect damage and predict cardiotoxicity. Deformation analysis seems to be a promising tool to detect myocardial dysfunction at an earlier stage [14].

Besides monitoring systolic function, it is recommend in cancer patients to perform a comprehensive echocardiographic evaluation measuring diastolic function and evaluating cardiac valves and pericardium [15].

Diastolic function is frequently impaired in cancer studies [4, 16]. Several studies demonstrated an early reduction in the e' velocity of the mitral annulus using tissue Doppler imaging (TDI), which remained reduced during and for several years after treatment [17, 18]. However, the use of the E/e' ratio remains questionable in the oncological setting because E and e' velocity fluctuations in these patients may be the consequence of changes in loading conditions associated with chemotherapy (e.g. nausea, vomiting, and diarrhoea) more than the result of a real change in left ventricle diastolic performance [4].

Chemotherapeutic agents do not directly affect cardiac valves, but valve heart disease may manifest in oncological patients for different reasons such as:

(a) Pre-existing valve disease
(b) Concomitant radiation therapy that causes calcification and fibrosis of the aortic root, aortic cusps, mitral valve annulus, tips, and commissures [19]
(c) Infective endocarditis favoured pancytopenia associated with chemotherapy
(d) Mitral regurgitation secondary to annular dilatation or apical tethering due to CRDT and tricuspid regurgitation as consequence of right ventricle dysfunction and pulmonary hypertension [3, 15].

Echocardiography is the assessment method of choice, and 3D echocardiography may be useful, particularly for the evaluation of mitral valve commissures. CMR and computed tomography (CT) may be used to assess the severity of the valve disease but usually are not required in routine clinical practice [15].

According to the current EACVI/ASE recommendations [15], patients with baseline or changing valve findings should undergo careful evaluation of valve structure and function during and after cancer treatment.

Pericardial disease is also common in oncologic patients, as consequence of cancer therapies or metastasis, and usually occurs as pericarditis and pericardial effusion and sometimes as constrictive pericarditis especially after radiotherapy or high-dose chemotherapy. Acute pericarditis may occur predominantly with the use of anthracyclines, cyclophosphamide, cytarabine, and bleomycin. Transthoracic echocardiography is the method of choice for the evaluation of patients with suspected pericardial disease due to chemotherapy, but CT can be helpful to identify calcification, and CMR should be considered in the evaluation of primary tumours of the heart. Pericardial effusion should be quantified and graded according to standard methods [20], and it is important to evaluate the presence of echocardiographic and Doppler signs of cardiac tamponade in this setting of patients.

Myocardial Deformation Imaging

LVEF reflects the volumetric variation of the ventricle during the cardiac cycle, which depends on the size and shape of the left ventricle, the contraction of the global myocardium, the integrity of the mitral and aortic valve, and the preload and post-load. In contrast, myocardial deformation analysis reflects the length variation of the myocardial fibres, and thus it is a measure of intrinsic contractility (Fig. 16.2, right panel) [14].

By the analysis of the motion of speckles in the two-dimensional ultrasonic image, this technique allows a non-Doppler angle-independent objective analysis of myocardial deformation, with the possibility to quantify longitudinal, circumferential, radial function and torsion. The best validated strain measure is global longitudinal strain (GLS). Speckle-tracking echocardiography (STE) has recently demonstrated to be an accurate, feasible, and reproducible measure of cardiac function [21].

The maximum extent of systolic myocardial deformation (i.e. peak systolic strain) and its

peak rate (i.e. peak systolic strain rate) were used regionally and globally [4]. One of the first studies using 2D-STE strain was performed in 2008 and demonstrated that this technique recognized early damage caused by anthracyclines [22].

Many authors subsequently focused their efforts on this topic to identify CTX in patients previously treated with oncologic therapies to predict CTX development.

2D-STE was more sensitive than LVEF reduction for the early recognition of asymptomatic left ventricle systolic dysfunction caused by chemotherapy in children and adults [4, 23–25].

Other studies [26, 27] provided information on serial evaluations of cardiac function before and after chemotherapy by comparing GLS with LVEF. They found that GLS was the most sensitive and specific measurement for the detection of subclinical myocardial injury early after anthracycline exposure (from 1 day to 3 months after the treatment in the different studies) because GLS decreased significantly without any reduction in LVEF.

A prospective study of 81 patients with breast cancer evaluated the use of longitudinal strain assessed at baseline, after completion of anthracycline-based therapy, and every 3 months during trastuzumab. A longitudinal strain value lower than −19% (less negative or a lower negative number) after the completion of anthracyclines was predictive of CTX [28]. The accuracy of the prediction increased when cardiac troponin was also measured [28]. Measuring the percentage variation of GLS between follow-up and baseline seems to be a specific approach to early detect CTX. Negishi K et al. demonstrated that an 11% reduction of GLS (95% confidence interval, 8.3–14.6%) was the optimal cut-off, with sensitivity of 65% and specificity of 94% for detecting CTX [29].

The European Society of Cardiology (ESC) recently provided a document [3] containing a practical approach for monitoring patients undergoing cancer therapy with GLS. Measurements of GLS during chemotherapy should ideally be compared with baseline value, and a relative percentage reduction of GLS of less than 15% from baseline is very likely to predict future CRTD (Table 12.1). The same vendor-specific ultrasound machine should be used when monitoring STE for longitudinal follow-up of patients with cancer.

A small study demonstrated that early therapeutic intervention with beta-blocker based on strain reduction alone allowed a normalization of strain values during follow-up; however evidences demonstrating a clinical impact of this approach are still lacking [30]. The multicentre, randomized SUCCOUR (Strain Surveillance During Chemotherapy for Improving Cardiovascular Outcomes) trial is designed to determine if a strain-based strategy for initiation of cardioprotective therapy is superior to one based on LVEF.

Three-dimensional speckle-tracking echocardiography (3D-STE) is a promising techniques in the evaluation of myocardial function. The possibility of evaluating the deformation on a full-volume model avoids the errors derived from the use of two-dimensional images [31].

Recent studies demonstrated that childhood cancer survivors evaluated by 3D-STE had significantly reduced GLS and torsion and greater systolic dyssynchrony index in comparison to healthy controls [32]. Mornoş et al. found that GLS evaluated by 3D-STE was superior to biomarkers and to LVEF in predicting future development of cardiotoxicity [33].

Although 3D-STE is a promising method, there are few studies on small populations that compared this technique to the other standard methods. Moreover, 3D-STE is not widely available in the echo-labs; thus its use has still to be considered reserved to research purpose.

Nuclear Imaging and Cardiac Magnetic Resonance

Radionuclide angiography (MUGA) was referred as the gold standard to evaluate left ventricle systolic function in patients undergoing chemotherapy for many years [34]. MUGA makes use of 99mTC-erythrocyte labelling enabling the visualization of the cardiac blood pool by γ-camera with electrocardiogram-triggered acquisitions.

The final result provides a highly reproducible and precise quantification of LV volumes and dyssynchrony independently of geometrical assumption [35]. The main disadvantage of MUGA is radiation exposure, which reduces its use given the increasing availability of other radiation-free imaging techniques (Table 12.1).

MUGA also provides limited structural and functional information on other cardiac structures (right ventricle, left and right atrium, valves, and pericardium). Therefore, it is frequently used as an adjunct and complementary technique to echocardiography.

The need of a reliable and accurate detection method for early CTX has encouraged the introduction of second-line advanced imaging modality into the evaluation of chemotherapy-treated patients, such as cardiac magnetic resonance (CMR) (Table 16.1). CMR is an ionizing radiation-free imaging method recently accepted as the gold standard for quantifying biventricular volumes, function, and mass [36, 37].

The standard CMR approach for quantifying biventricular function parameters uses contiguous short-axis slices covering the entire ventricles acquired from a cine steady-state free precession (SSFP) sequence (Fig. 16.3) [36]. In the evaluation of CTX, the incremental value of CMR is represented by its capability for providing information on tissue characterization, such as oedema, hyperaemia, fibrosis, and iron overload. It also serves to evaluate the pericardium, especially in patients with chest irradiation.

Neilan et al. [38] showed that myocardial scar by late gadolinium enhancement CMR is infrequent in patients with anthracycline cardiomyopathy despite a reduced ejection fraction, and indexed LV mass by CMR imaging is a predictor of adverse cardiovascular events.

A new CMR parameter was recently proposed, the LV global function index, that combines left ventricular stroke volume, end-systolic and end-diastolic volumes, and mass, and a value less than 37% has been shown to be associated with the occurrence of cardiovascular events [39]. However, no data are available on this promising index in monitoring CTX [36].

Myocardial deformation can be evaluated by tagging techniques and, more recently, by using phase-contrast imaging. In the technique most frequently used, the myocardium is tagged with a grid of magnetic saturation lines at end diastole, allowing the analysis of deformation by tracking the distortion of the grid during systole.

In a recent study [40], measures of left ventricular systolic performance (LVEF and mean mid-wall circumferential strain) deteriorated

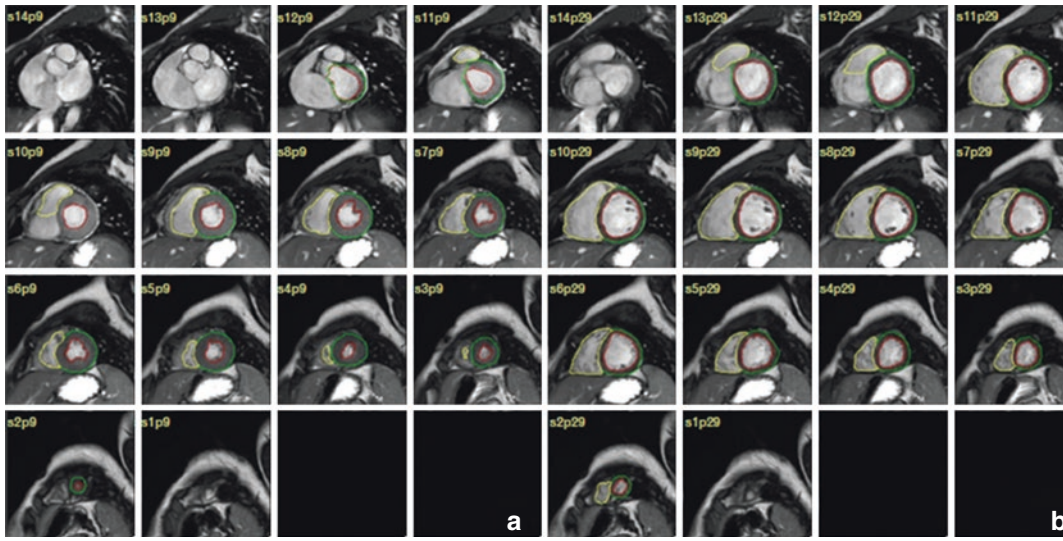

Fig. 16.3 Quantification of biventricular function by CMR. (**a**) End-systolic phases; (**b**) end-diastolic phases

early and remained abnormal 6 months after initiation of low to moderate doses of anthracycline-based chemotherapy. Authors did not appreciate new infarcts or fibrosis by late gadolinium enhancement.

Few studies evaluated the presence of oedema and fibrosis in patients treated with chemotherapy. Regarding the detection of myocardial oedema as early marker of cardiac damage, in this setting of patients, results are contrasting, and no prognostic data are available [41, 42].

The prevalence of non-ischaemic areas of LGE was reported between 6% and 100% [43, 44]. However, the role of the LGE in the prognostic stratification of these patients is not yet well defined [38, 44, 45].

LGE is able to detect only macroscopic fibrosis. However, oncologic patients can develop diffuse myocardial fibrosis that can be detected by T1 mapping with the evaluation of the extracellular volume (ECV). Small studies showed encouraging results on the use of T1 mapping in the detection of myocardial damage during and after chemotherapy [46–48].

Based on these evidences, T1 mapping seems to be a very useful technique in oncologic patients in order to detect changes in the molecular features of the myocardium prior to the occurrence of functional alterations. However, its prognostic role is still under investigation.

Cardiac damage induced by anthracyclines appears to be partially dependent on the alteration of intracellular iron metabolism. Unfortunately, evaluations of myocardial iron overload in patients treated with anticancer drugs have not yet been performed [36].

Actually, CMR is recommended for the quantification of LVEF when the quality of echocardiogram is suboptimal. In follow-up assessments, CMR is recommended for the quantification of LVEF in cases of possible discontinuation of chemotherapeutic regimens as a result of CTX or when LVEF estimation by echocardiography is controversial or unreliable due to technical constrains. Diastolic function by CMR is not usually recommended in current practice [15].

Biomarkers

The use of cardiac biomarkers during cardiotoxic chemotherapy may be considered in order to detect early cardiac injury. Currently, the most studied biomarkers for the early detection of cardiac damage induced by anticancer drugs are cardiac troponins (cTns) and natriuretic peptides (Table 16.1).

Cardiac troponins are sensitive and specific markers of myocardial injury and are widely used in cardiovascular medicine. Troponin I is a serum marker that detects damage of myofibrils and cardiomyocytes. It identifies acute injury due to ischaemia but also to other causes such as drugs.

Among troponins, TnI is the most widely studied serum biomarker of cardiotoxicity, its elevation can predict the future decline of myocardial function, and the amount of its elevation is correlated with patients' prognosis [49]. Particularly, it has been shown that in patients with cancer, treated with high doses of anthracyclines, the increase in cTn allows discrimination between patients with a low risk of developing chemotherapy-induced CTX and who do not need strict follow-up and those at high risk, which require a more rigorous cardiac monitoring [50].

In particular, patients with a persistent (early and late) increase in cTn show a greater reduction in LVEF at follow-up [51]. In patients treated with trastuzumab, the elevation of cTnI identified patients who developed CTX and who did not recover after interruption of treatment [52]. Less established is the role of troponin in predicting cardiotoxicity in patients treated with conventional doses of anthracyclines; in this setting high-sensitivity troponin (hsTn) is probably more useful (Table 16.2).

In patients with breast cancer, a recent study demonstrated that the combination of high-sensitivity troponin with GLS might provide the greatest sensitivity (93% when both are altered) and sensitivity (87%, when one of two parameters is altered) to predict future cardiotoxicity [28].

Main advantages of cTn use include wide availability, accuracy, reproducibility, and lower cost than imaging. Nevertheless, there are some uncertainties that still remain unre-

Table 16.2 Main studies evaluating the conventional and emerging biomarkers in the detection of cardiotoxicity (CTX)

Authors	Population	Results
Sawaya et al. [28]	82 patients with breast cancer treated with anthracyclines, taxanes, and trastuzumab who were evaluated every 3 months with echocardiography (strain) and blood sample (hsTnI, NT-proBNP, and ST2)	Myocardial strain and hsTnI, measured at the completion of anthracycline therapy, are useful in the prediction of subsequent cardiotoxicity
Ky et al. [53]	78 patients with breast cancer treated with doxorubicin and trastuzumab who were evaluated every 3 months for different biomarkers	Early increases in TnI and MPO levels offer additive information about the risk of cardiotoxicity in patients undergoing doxorubicin and trastuzumab therapy
Cardinale et al. [50]	251 patients with breast cancer treated with TZT with or without other chemotherapy (197 had prior exposure to anthracyclines)	TnI identifies patients at risk for developing cardiotoxicity and who are unlikely to recover following the completion of therapy
Cardinale et al. [51]	703 patients with various malignancies treated with high-dose chemotherapy. TnI measurement before chemotherapy at 1, 3, 6, and 12 months after the end of the treatment and every 6 months thereafter	Elevated TnI (cut-off >0.08 ng/mL) identified patients at greater risk of cardiac events (particularly the group with persistently elevated TnI)
Feola et al. [54]	52 patients with early breast cancer treated with anthracyclines	In patients who developed left ventricular systolic dysfunction, BNP but not TnI increase was observed
Suzuky et al. [55]	27 patients receiving anthracyclines are investigated by serial measurements of BNP, A-type natriuretic peptide, renin, aldosterone, angiotensin II, norepinephrine, epinephrine, and echocardiography	BNP levels are elevated after anthracycline administration. Patients with persistent elevations showed a poor prognosis
Sandri et al. [56]	NT-proBNP was measured after chemotherapy treatments in 52 patients affected by aggressive malignancies	Persistently increased NT-proBNP early after administration of HDC is strongly associated with development of cardiac dysfunction
Romano et al. [57]	71 patients who did not undergo high-dose chemotherapy with anthracyclines. NT-proBNP and cTnI level measurement before and 24 h after each cycle	NT-proBNP, but not troponin, showed abnormal values. LV impairment was significantly worse in patients with persistently elevated NT-proBNP levels
Lagoa et al. [58]	Measurements of the temporal evolution of selected biochemical markers after treatment of rats with doxorubicin (20 mg/kg body weight)	Quinone oxidoreductase-1 activity and increase of hydrogen peroxide production by NADPH oxidases are early biomarkers in doxorubicin cardiotoxicity
El Ghandour et al. [59]	In 40 NHL patients who received doxorubicin, human heart-type fatty acid-binding protein (H-FABP) was assessed 24 h after the first cycle of chemotherapy	H-FABP may serve as a reliable early marker for prediction of cardiomyopathy induced by doxorubicin
Horacek et al. [60]	53 patients undergoing HCT for various haematological malignancies	Increased release of GPBB could be considered a sign of acute subclinical CTX
Horie et al. [61]	Evaluate the role of miRNAs in acute Dox-induced cardiotoxicity in mice	When miR-146a "decoy" genes were introduced into cardiomyocytes, ErbB4 expression was up-regulated, and Dox-induced cell death was reduced

GPBB glycogen phosphorylase isoenzyme BB, *HCT* haematopoietic cell transplantation, *HDC* high-dose chemotherapy, *hsTnI* high-sensitivity troponin I, *LV* left ventricle, *MPO* myeloperoxidase, *NHL* non-Hodgkin lymphoma, *NT-proBNP* N-terminal fragment B-type natriuretic peptide, *TnI* troponin I, *TZT* trastuzumab

solved, including the optimal timing of assessing, frequency of cTn evaluations, optimal cut-off point for positivity with the highest level of specificity, and comparison of different assays of troponin [49]. Table 12.2 reports main studies which demonstrated usefulness of TnI for predicting CTX.

Natriuretic peptides are hormones released during haemodynamic stress when ventricles dilate, undergo hypertrophy, or is subject to increased wall tension. Use of BNP and NT-proBNP to detect subclinical cardiac dysfunction is under investigation, and results of published studies are controversial [54, 62, 63].

BNP levels were increased during chemotherapy treatment and correlated with diastolic dysfunction [55] and progressive development of cardiac dysfunction [56, 64].

In some studies, BNP anomalies were observed in the absence of changes in cTn [57, 65, 66], which suggested that in patients receiving anticancer drugs at low or medium doses and with a predictable reduced myocardial suffering, BNP monitoring could be more useful than cTn [49]. In other studies, BNP was not predictive of EF change [28].

Other *circulating biomarkers* tested include C-reactive protein, cytokines, and parameters of oxidative stress.

Due to the mechanisms of anthracycline-mediated toxicity, measurement of inflammatory markers and parameters of oxidative stress are also reasonable [49, 58]. *C-reactive protein* is a nonspecific marker of inflammation, and the utility of its evaluation in the setting of anticancer drug-related CTX is controversial.

Recently, *galectin-3* (gal-3) has been considered as a potential biomarker for predicting early or late onset of CTX. However, increases of gal-3 were found to be insignificant and not predictive of CTX as defined by echo-derived LVEF reduction [53].

Finally, potential CTX markers under investigation in oncology are heart-type fatty acid-binding protein (H-FABP), glycogen phosphorylase BB (GPBB), and circulating microRNAs, but they are not yet validated [59–61].

Multimodality Approach

As demonstrated by recent studies, a combined multimodality approach in selected individuals may provide incremental value in predicting cardiotoxicity and prove to be useful in clinical practice [28, 53, 67–69]. However, only a few studies have explored the utility of a multimarker approach in monitoring patients undergoing antineoplastic drugs at high baseline risk.

Fallah-Rad et al. [43] conducted the first multimodality surveillance strategy, combining biomarkers (troponin T, CRP, and BNP) with imaging (echocardiography and CMR) in breast cancer patients treated in the adjuvant setting by anthracyclines and trastuzumab. Biomarkers were not associated with any prognostic value, along with LVEF assessment, but Doppler measurement of *s′*, GLS, and radial strain parameters were able to identify, at 3 months' follow-up, the patients who developed CTRCD at 6 months. In this study, CMR, performed at baseline and at 12 months, documented an increase in LV volumes, a decrease in LVEF, and a late gadolinium enhancement in the LV lateral wall in the CTRCD group.

Similarly, Sawaya et al. [18] observed that NT-proBNP was not associated with any predictive value, while high-sensitive TnI at 3 months appeared as an independent predictor of cardiotoxicity at 6 months. Furthermore, a combination of GLS and hsTnI allowed with a better accuracy the early identification of myocardial damage and was predictive of subsequent CRTCD during the surveillance in patients receiving trastuzumab after anthracyclines.

The troponin levels added prognostic value to GLS: if both were abnormal, the specificity for the prediction of CTRCD increased from 73% to 93%. If both were normal, the negative predictive value increases to 91% [28].

Given these scientific evidences, the recent EACVI/ASE consensus document [15] encourages an integrated approach to early detect cardiotoxicity. Particularly a strategy that includes, in addition to LVEF assessment, the calculation of GLS and the measurement of troponin at baseline and during follow-up in order to compare changes during time is proposed. (Fig. 16.4).

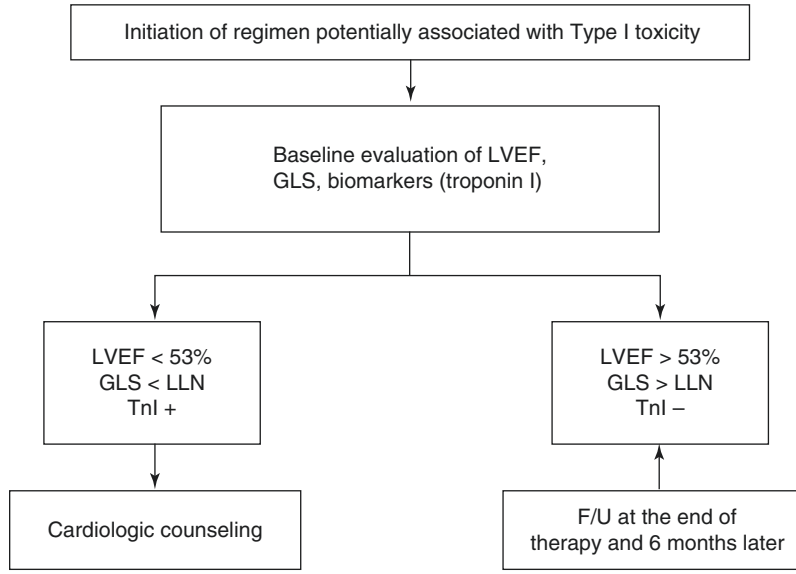

Fig. 16.4 Multimodality approach to monitor patients undergoing antineoplastic treatment. 2DE, 2D echocardiography; 3DE, 3D echocardiography; GLS, global longitudinal strain; LLN, lower limit of normal; LVEF, left ventricular ejection fraction. (Reprinted from Plana et al. [15]. With permission from Elsevier)

Conclusions

Systematic and repeated monitoring of LVEF remains the most used technique to diagnose cardiotoxicity in clinical practice. 2DE is the most used method; however, 3DE has proved to be more accurate and reproducible, and this is preferable if available. Regarding CMR, it is very accurate, but its low availability and the high cost limit its use to particular subsets of patients.

Decrease of LVEF is detectable when damage is considerable and possibility of recovery reduced; therefore it is not suitable as an early indicator of cardiotoxicity.

Among the new techniques that evaluate cardiac function, GLS derived by 2D-STE is the best validated technique with a considerable amount of evidences supporting its role in the detection of cardiotoxicity. Baseline evaluation of GLS and periodical monitoring during treatment is recommended. Promising techniques such as 3D-STE and tissue characterization performed by CMR are under investigation and could provide new insights into the future for the evaluation of chemotherapy-treated patients.

Monitoring troponin levels also appears to be effective in the prediction of cardiotoxicity, and its elevations identify high-risk cohort of cancer patients who may benefit from early cardioprotective medication. According to some evidences, the persistence of NT-proBNP elevation seems to identify patients at higher risk of LVEF decline.

A multimodality approach using troponin and GLS seems to increase the accuracy in the detection of cardiotoxicity especially in patients at high baseline risk; however further studies are needed for wider validation in the clinical setting.

Cardiotoxicity is likely to be a continuous phenomenon characterized by progressive left ventricular ejection fraction decline that, if disregarded and not treated, may progressively lead to overt heart failure. On the other side, if we catch this process in the early phases, overt damage can be prevented and the dysfunction avoided. For this reason, it is extremely important to monitor patients undergoing antineoplastic drugs and to apply sensitive technique to early detect damage.

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Diagnosis of Cardiac Damage: Role of Stress Echo

17

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Introduction

Chemotherapy treatments are a recognized cause of direct adverse effects on cardiovascular system [1], leading to a progressive cardiac dysfunction and symptomatic heart failure [2].

Cardiovascular toxicity of anticancer drugs can result as an early (acute) effect, within the first year of treatment, or as a late effect, developing through years after therapy [3, 4]. The incidence of overt heart failure in patients undergoing anticancer treatment is 2–5%. Conversely, the rate of patients developing asymptomatic left ventricular (LV) damage is 15–18% [5, 6]. In this scenario, great attention is constantly growing on the detection of early sign of LV dysfunction, both during therapy and follow-up of oncologic patients.

Anthracycline detrimental effect is a well-known cumulative, dose-related cause of progressive cardiac dysfunction [7, 8]. Additionally, though new targeted agents (such as monoclonal antibodies and tyrosine kinase inhibitors targeting HER-2, VEGF and VEGF receptors) have effectively improved chemotherapy efficacy, they could bring to different degree of cardiac damage. Of note, cardiac damage provoked by the target therapy may be additive when associated with anthracycline [9, 10]. The utility of electrocardiography, standard and advanced echocardiography (speckle tracking analysis and three-dimensional echo) and nuclear imaging techniques at rest as well as of cardiac biomarkers for early diagnosis of heart involvement has been broadly proven in this clinical setting [11–16]. In this context, stress echocardiography represents an additional, effective test, able to reveal occult LV dysfunction and coronary artery disease (CAD), particularly in patients at intermediate or high pretest probability [17, 18]. Considering the late effect of cancer treatment on the heart, cardiac stress testing can unmask subclinical coronary stenosis and subtle myocardial dysfunction as well.

Utility of Cardiac Stress Test

A definite and commonly shared screening follow-up in order to detect cardiac effects of cancer treatment, even when asymptomatic, is of paramount relevance. Stress echocardiography appears to be most beneficial in anticancer-treated populations, particularly in detecting anthracycline-induced subclinical LV dysfunction [19, 20]. Notably, it can drive rapid cardiac intervention in terms of both chemotherapy

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dosage reduction and cardio protective strategies. Exercise or pharmacological stress echocardiography is frequently used for its diagnostic and prognostic values [21, 22]. It has been used for long-term screening in childhood cancer survivors. Khouri et al. [20] showed that LV contractile reserve, expressed by change of LV global longitudinal strain (GLS) from rest to peak exercise, was significantly lower in patients undergoing anthracycline-based treatment for breast cancer when compared to healthy controls. Civelli et al. [19] demonstrated the capability of dobutamine stress echocardiography in detecting subclinical LV dysfunction during high-dosage anthracycline chemotherapy in adult women affected by breast cancer. Reduction of LV contractile reserve as the difference of LV systolic function between stress and rest was observed in patients undergoing chemotherapy treatment even before the third cycle of high-dosage anthracycline therapy. A low LV contractile reserve (≥10% drop from baseline of LVEF below the cut-off value of 50%) was identified as a prognostic indicator below the traditional parameters of cardiotoxicity.

Nowadays radiotherapy is frequently used associated to chemotherapy to reduce cancer extent and minimize the risk of recurrences. Indeed mediastinal irradiation is mainly involved after conservative or radical breast surgery in the context of adjuvant therapy, adjuvant or exclusive radiotherapy of lung and oesophageal cancer, and as a complement to systemic treatment in lymphoma. Nevertheless, high-dose radiation exposure on the thorax can boost the chemotherapy damage on cardiovascular system resulting in microvascular and macrovascular injury and accelerated atherosclerosis of coronary arteries, valvular abnormalities and myocardial fibrosis, pericardial inflammation or effusion [23–26]. Of note, there is an increment of 1.27 risk of heart disease in patients treated with radiation for breast cancer compared to those who were not [27]. In this context, stress echocardiography can detect significant CAD in asymptomatic patients after mediastinal irradiation [28]. Patients at increased risk of coronary events after 5–10 years following radiotherapy (Table 17.1) could be addressed towards a functional stress test to exclude obstructive CAD. Accordingly, stress echocardiography should be planned every 5 years if a given patient does not show abnormalities at the first stress echocardiography or remains asymptomatic [29].

Table 17.1 Risk factor of cardiovascular disease in patient treated with radiotherapy

High cumulative dose of radiation (>30 Gray)
Younger patients (<50 years)
High dose of radiation fractions (>2 Gray/day)
Presence and extent of tumour in or next to the heart
Lack of shielding
Concomitant chemotherapy
Cardiovascular risk factors: Diabetes mellitus Smoking Overweight Moderate/severe hypertension Hypercholesterolaemia
Pre-existing cardiovascular disease

High-risk patients are defined as patients with chest irradiation with ≥1 risk factor mentioned above

Types of Stressors

Indications for stress echocardiography may be generally summarized as follows: (i) suspect of coronary artery disease (CAD) (presence of chest pain or unexplained dyspnoea), (ii) evaluation of newly diagnosed LV dysfunction and (iii) assessment of new-onset valvular heart disease (following radiotherapy). The stressors mainly used to detect alteration of LV function induced by chemotherapy are exercise, dobutamine and dipyridamole [30]. Table 17.2 shows sensitivity and specificity of different stressors test in detecting CAD in the general population [31]. Of interest, electron beam computed tomography (EBCT) and single-photon emission computed tomography (SPECT) appear to have a higher sensitivity but a relatively lower specificity when compared with stress echocardiography. Consequently, in patients at intermediate or high pretest probability, in which guidelines suggest to perform functional stress test [17, 18], stress echo could be preferred in relation with higher specificity. It has also to be taken into account that EBCT and

SPECT should be used cautiously for follow-up studies considering the cumulative radiation exposure in patients who have already undergone radiation therapy [32].

Exercise echocardiography can be done by two different modalities: treadmill or cycle ergometer. The latter allows to perform a continued echocardiographic monitoring, thus avoiding false negative that may occur using treadmill. By both the modalities, exercise echo provides prognostic and diagnostic information, also allowing an evaluation of oxygen consumption, heart rate and blood pressure response. Of interest, exercise test is the safest stressor, with occurrence of major life-threatening effects (myocardial infarction, ventricular fibrillation) fivefold less than dipyridamole and tenfold less than dobutamine [33–36]. Dobutamine acts directly on both beta-1 and beta-2 adrenoceptors, increasing heart rate, blood pressure and inotropic activity, that is, the oxygen consumption. Low-dose dobutamine (5–10 μg/kg/min) stress echo is one of the preferred stress tests to assess myocardial viability [37]. A viable myocardium may reflect the presence of significant CAD in patients with LV dysfunction who could need coronary reperfusion. Stress echo evaluating coronary flow reserve (by high-dose dipyridamole) allows to quantify the response of flow in the distal tract of the left anterior descending artery to a maximal vasodilation (Fig. 17.1) and identify possible contemporary regional wall motion abnormalities [38–40]. Dipyridamole acts as vasodilator that, by stimulating the A2a adenosine endothelial receptors, reduces myocardial oxygen supply through the "steal" phenomena of the coronary collateral circulation.

Stress echo by cold pressure test evaluates mainly endothelial-derived coronary flow reserve function, avoiding additional cost and relevant pharmacological side effects. However, the true clinical usefulness of cold pressure test is still debated and is actually mainly used for research purpose.

Table 17.2 Sensitivity and specificity of different functional stress test in detecting cardiovascular disease in the overall population

Stressor	Sensitivity % (95% CI)	Specificity % (95% CI)
Exercise	83 (80–85)	84 (80–88)
Dobutamine	81 (79–83)	84 (82–86)
Dipyridamole	72 (69–75)	95 (93–96)
Exercise SPECT	88 (85–90)	69 (63–75)
Dipyridamole SPECT	90 (87–93)	75 (66–85)
EBCT	93 (91–96)	54 (45–64)

Adapted from Heijenbrok-Kal et al. [31]
EBCT electron beam computed tomography, *SPECT* single-photon emission computed tomography

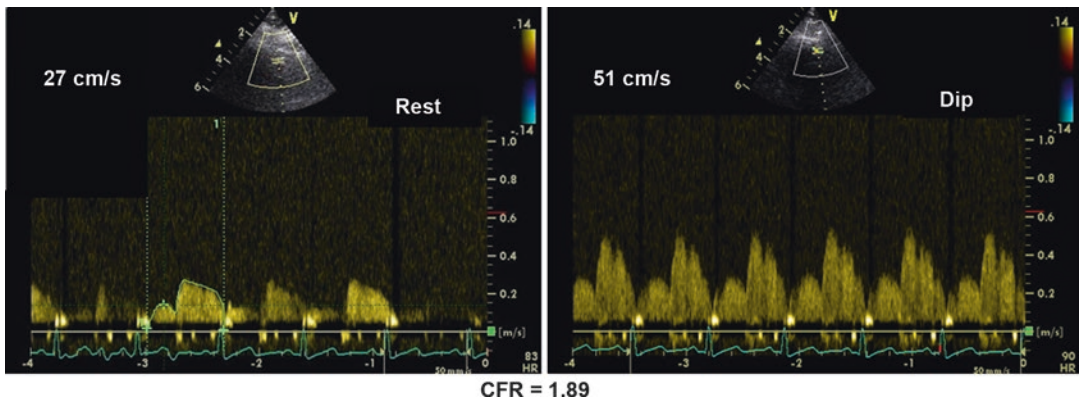

Fig. 17.1 Dipyridamole stress echo performed in a patient affected by colon-rectal cancer treated with anti-VEGF (bevacizumab). The purpose of this study was to assess the endothelial response after treatment in patient referring atypical angina. On the left panel coronary flow at rest; end-diastolic peak: 27 cm/s. On the right panel coronary flow after dipyridamole infusion end-diastolic peak: 51 cm/s. As a result coronary flow reserve was reduced (CFR = 1.89; normal value >2.0) revealing an alternated endothelial response

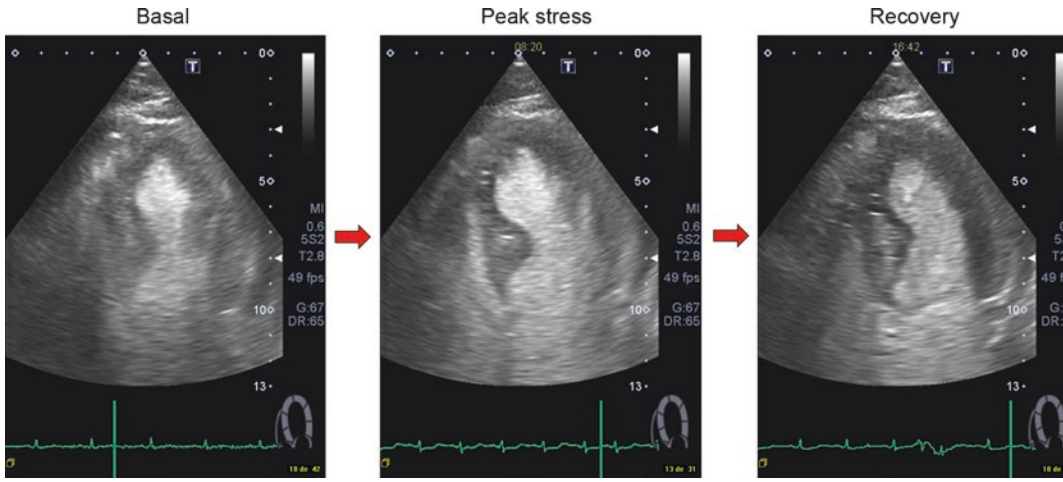

Fig. 17.2 This figure shows a contrast-enhanced eco stress in a survival patient with history of Hodgkin's lymphoma treated with chemo-/radiotherapy that refers new-onset exertional dyspnoea. Contrast-enhanced stress echo allows to better detect endocardial border and, consequently, wall motion abnormalities. Left panel: after contrast injection apical four chamber view at rest. Central panel: contrast-enhanced peak stress (dobutamine 40 μg/kg/min); it is evident a left ventricular dilation at end-systole and hypokinesia of mid-apical segment of the septum. The patients at this stage referred chest pain. Right panel: contrast-enhanced recovery acquisition; at this stage the wall motion alterations receded as well as the symptoms

Since sensitivity and specificity of different stressors are almost comparable, in cancer patients, the choice of the stressor can be selected according to several factors. Firstly, cancer patients, who currently undergo chemotherapy, are usually affected by malaise, muscle pain and fatigue (generally as a consequence of the antineoplastic regimen). Exercise echo, despite easy to perform, cheap and very safe [41], cannot be performed in all cancer patients who often present fatigue frequent and different kinds of physical limitations. Secondly, effects of certain cancer treatments, which can induce ventricular fibrillation (cyclophosphamide, cisplatin, anthracycline) and atrial fibrillation (bortezomib, vinca alkaloids) or also prolong the QT interval (e.g., tyrosine kinase inhibitors), should be carefully taken into account to avoid dobutamine [42]. Conversely, the assessment of coronary endothelial function (through dipyridamole or cold pressure test) could be preferred in patients undergoing anticancer treatments which produce direct endothelial damage (5-fluorouracil) or endothelial dysfunction through nitrite oxide inhibition (VEGF inhibitors).

Worthy of note, pharmacological stress echocardiography almost doubles the cost of standard echocardiography at rest but can be considered able to provide a good overall cost-effectiveness for diagnosis and management in cardiovascular disease [43].

Frequently cancer patients may present suboptimal echo window due to chest radiotherapy, thorax surgery or mediastinal masses [16]. Accordingly, contrast-enhanced stress echocardiography can be preferred (either pharmacological or exercise-stress-induced test) to improve endocardial border delineation under these circumstances (Fig. 17.2) [18, 44].

What and How to Measure

Although the absence of changes during time of the most common clinical parameter of LV function, resting LVEF, is commonly considered synonym of normal LV function and absence of cardiotoxicity, the myocyte damage can be present before changes of LVEF become overt [45]. Significant change in LVEF at rest may be rather sign of irreversible damage of heart function.

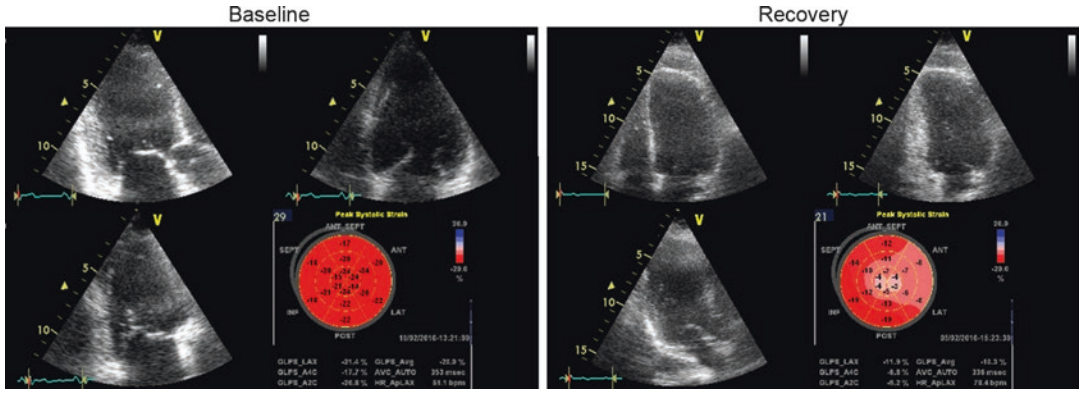

Fig. 17.3 Woman affected by left side breast cancer, smoker, history of left side radiotherapy. During last cycle of antineoplastic treatment based on anthracycline (doxorubicin), she refers effort chest pain. Dobutamine stress echo was performed. On the left panel speckle tracking analysis at rest. Global longitudinal strain results −20%. On the right panel speckle tracking analysis computed during the first minute of recovery. The patients accused chest pain irradiated to the jaw. Speckle tracking analysis after dobutamine infusion showed hypo-/akinesia of the apex and the anterior and lateral wall. The patients were sent to the cath-lab that revealed an ostial lesion of the left anterior descending artery

Accordingly, exercise stress for evaluating changes of LVEF dramatically increases the sensitivity for detection of anthracycline-induced LV dysfunction [46]. However, myocardial strain can better represent the effective myocardial function and results to be more sensitive to identify possible changes of both regional and global LV function. Strain imaging has been recently applied to stress echocardiography (Fig. 17.3) [47, 48]. Strain and strain rate have recognized diagnostic and prognostic value in the evaluation of anthracycline-induced LV dysfunction at rest, enough to be included in recent ASE/EACVI recommendations on early detection of cardiotoxicity [17, 18]. Several parameters such as GLS or also some surrogates of LV longitudinal function such as pulsed tissue Doppler-derived systolic and diastolic velocities of the mitral annulus can be utilized during stress [19, 20]. These parameters are all associated with negative outcomes. Cardiac stress test raises the sensitivity of both LVEF and GLS at rest (Table 17.3) [19, 20, 49]. Moreover, the absence of LV contractile reserve, i.e., no change or a decrease in LVEF during stress echo, is concomitant to decrease of myocardial coronary flow and oxygen consumption that represents a predictor of heart failure in survival patients [50]. Of interest, Yildirim et al. demonstrated that in asymptomatic long-term cancer survivors treated by anthracycline, dobutamine stress echo unmasked significant alteration of systolic and diastolic function calculated with tissue Doppler-derived velocities of both mitral and tricuspid valves [51]. This finding suggests that the analysis of myocardial longitudinal function may be applied to stress echo even in echo-lab without experience in more advanced technique such as STE.

Table 17.3 Echo parameters that show predictive value during echocardiography functional stress test

Measurement	Cut-off value
Peak LVEF (%)	<50%
LVCR (based on EF)	<5[a]
LVCR (based on GLS)	<3[a]

CR contractile reserve, *EF* ejection fraction, *GLS* global longitudinal strain, *LV* left ventricle
[a]Absolute value

New Technologies and Future Prospective

New data has been recently gathered on the application of three-dimensional echocardiography in the functional stress test [52]. Ideally, the introduction of real-time (RT) three-dimensional stress echocardiography (3DSE) overcomes several limitations of two-dimensional

Table 17.4 Main advantages and limitations of RT 3DSE versus 2D stress echocardiography

Advantages	Limitations
Shorter acquisition time Less operator-dependent More reproducible Precise alignment/ anatomically correct tomography section Full volume acquisition of entire true left ventricle	Lower spatial and temporal (volume/frame rate) resolution especially in peak stress Influenced by respiration, patient motion and variation in heart rate causing artefacts Suboptimal anterior and lateral wall visualization Longer offline data analysis time

stress echocardiography (Table 17.4). In fact, it allows the evaluation of the entire ventricle at the same time avoiding temporal assumptions during the assessment of the results. Furthermore, RT-3DSE is less operator-dependent, thus potentially increasing the efficiency of the echo laboratory [53]. Both exercise and pharmacologic-induced 3DSE appear to be highly reproducible, resulting in better interobserver agreement when compared to 2D exam [54–56]. However, this technique shows several limitations, mainly due to its relatively lower spatial and temporal resolution. The multi-beat acquisition, which can be done at rest to improve the imaging resolution (frame/second), found laborious application during exercise test because it implies the need of a patient's apnoea to avoid artefact of acquisition ("stitching"). Other limitations of RT-3DSE include the poor anterior and lateral wall visualization due to large footprint of the matrix transducer that causes rib shadowing, particularly in large heart cavities (e.g. cardiomegaly). Finally, long offline data analysis may be time consuming and adversely affects the workflow for a rapid evaluation of stress echo.

Conclusions

In the oncologic patients, stress echocardiography presents two main applications. Firstly, it can be successfully used to identify subclinical, early LV dysfunctions in patients at risk for overt heart failure. For this aim, physical stress exercise should be preferred, using traditional parameters or, better, advanced techniques mainly represented by GLS. Moreover, stress echocardiography can be very useful for diagnosing CAD in patients undergoing cancer drugs potentially promoting myocardial ischaemia and, even several years after completion, in patients experiencing radiotherapy. For this aim, the combination of visual assessment of regional wall motion could be improved substantially by the use of quantitative evaluation of regional longitudinal strain. Application of 3D echocardiography to the functional stress echo could be promising, allowing the evaluation of the overall LV wall motion simultaneously with higher reproducibility. Further studies will be needed to promote the clinical use of those advanced techniques during the performance of stress echocardiography in oncologic patients.

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18 Early Detection and Monitoring of Vascular Damage

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Introduction

Vascular damage is one of the various adverse effects related to the oncologic therapy. Anticancer drugs that interfere with the vascular growth factor pathway have direct detrimental vascular effect, e.g., arterial hypertension, and can induce arterial event such as thromboembolism. This effect can be accelerated in the presence of traditional cardiovascular risk factors, underlying a possible vascular component to the etiology. Several mechanisms have been evocated to explain vascular toxicity, including dysfunction of damage of endothelial cells, increased platelet aggregation, and alteration of nitric oxide (NO) levels resulting in vasospasm. Table 18.1 lists the main anticancer drugs inducing adverse vascular effects. Vascular toxicity can be divided in two classes: type I (sustained injury) and type II (transient dysfunction) [1]. Table 18.2 lists the main anticancer drugs associated with type I and II vascular toxicity. Type II vascular dysfunction, which reflects coronary and peripheral vasospasm and finds relief in vasodilator therapies, requires careful attention in the acute phase. Conversely, type I vascular toxicity needs a well-planned, long-term follow-up. These different types of vascular damage can determine a broad spectrum of pathological conditions (arterial and venous thrombosis) which may become clinically overt in short-term periods or even appear progressively (peripheral vascular disease, stroke, coronary artery disease). Accordingly, vascular imaging tools shall be promoted for detecting early these manifestations and driving patient's management.

Arterial and Venous Thrombosis

The incidence of arterial thrombotic events is about 1% in cancer patients. The concomitant presence of solid tumors such as metastatic pancreatic, breast, colorectal, and lung cancers treated by anthracyclines, taxane, and platinum represents well-defined risk factors for arterial thrombotic event [2]. Cancer is an intrinsic prothrombotic condition which can also predispose to atrial fibrillation, a disease which can itself induce embolic dissemination. Moreover, some target anticancer drugs, such as VEGF inhibitors and anti-BCR-ABL TKI, appear to facilitate thromboembolic complications [3]. Even some hormonal deprivation therapies (aromatase inhibitors), which have demonstrated to reduce substantially cancer recurrence and improve survival in women with breast cancer or men with prostate

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Table 18.1 Different anticancer drugs inducing adverse vascular effects

Treatment	Endothelial cell apoptosis	Oxidative stress	Inflammation	Coagulation disorder-thrombotic state	Endothelial-dependent vasodilation
Alkylating agents					
Platinum compounds	Direct toxic effect	Free radical generation	Activate mononuclear cells, leukocyte	Platelet aggregation Increased fibrinolysis	Decreased NO levels
Cyclophosphamide	Direct toxic effect			Platelet aggregation	Decreased ACE levels
Antibiotics					
Anthracyclines	Caspase-mediated apoptosis	ROS-induced dysregulation of superoxide levels		Decrease ET-1 levels	Decreased endothelium-dependent relaxation
Bleomycin	Fas ligand upregulation				Decrease NO level
Vinca alkaloids	Caspase-mediated apoptosis		Inhibition of the anti-inflammatory NO effect	Decrease ET-1 levels	
Taxanes	Induction of endothelial apoptosis		Increase level in TNF-α	Decreased thrombomodulin	Impaired NMD
Antimetabolites					
5-Fluorouracil	Direct endothelial injury		Increase cytokine level	Shift to prothrombotic state	Toxic effect on NO synthase Vasoconstriction via protein kinase C
Methotrexate	Direct apoptotic effect			Hyperhomocysteinemia	
VEGFR inhibitors		Production of superoxide anion	Inhibition of the anti-inflammatory NO effect		Inhibition of endothelial NO synthase

ACE angiotensin-converting enzyme, *ET-1* endothelin 1, *NMD* nitrate-mediated vasodilation, *NO* nitric oxide, *ROS* reactive oxygen species, *TNF-α* tumor necrosis factor-alpha, *VEGFR* vascular endothelial growth factor receptor

Table 18.2 Type I and type II vascular toxicity of anticancer drugs

	Type I	Type II
Characteristic	Sustained vascular toxicity	Transient vascular toxicity
Mechanisms	Endothelial injury and apoptosis	Endothelial dysfunction Vascular smooth muscle cell dysfunction
Drugs	Cisplatin Bleomycin Vincristine Nilotinib Ponatinib	5-Fluorouracil Capecitabine Everolimus Bevacizumab Rituximab

Table 18.3 Predictive model for chemotherapy-associated VTE

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Pre-chemotherapy platelet count 350 × 10^9/L or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Pre-chemotherapy leukocyte count more than 11 × 10^9/L	1
BMI 35 kg/m^2 or more	1

Modified from Khorana et al. [7]

cancer, appear to increase the incidence of arterial thrombotic events [4]. Radiotherapy may also affect big vessels (e.g., aorta) and other peripheral arteries that are involved in the radiation field, thus resulting in ischemic limb manifestations. Notably, this process can give clinically overt manifestations even after 10 years after the beginning of radiotherapy.

Venous thrombosis and venous thromboembolism (VTE) are very frequent in cancer patients. Cancer therapy can play an important role in facilitating VTE. Concomitant administration of chemotherapeutic agents and VEGF inhibitors increases sixfold the risk of VTE and twofold the risk of recurrent VTE [5]. Also the hormonal therapy with tamoxifen increases VTE rate when compared with aromatase inhibitors [6]. The use of indwelling catheters, largely used for the administration of different kinds of anticancer drugs, and in particular the individual patient's risk of venous thrombosis at baseline, i.e., before the beginning of anticancer therapy, represent other important determinants of VTE etiology.

There is no evidence that a screening strategy may prevent thrombotic event. Worthy of note, Khorana et al. [7] suggested a risk model to stratify patients at risk for thrombosis that include cancer type (location) and baseline platelet and leukocyte count, hemoglobin level, and body mass index. This score stratifies into low- (score 0), intermediate- (score 1–2), and high-risk patients (score >3) in order to guide eventual thrombophylaxis therapy (Table 18.3). In the suspicion of venous thrombosis, the diagnostic test of choice for deep venous thrombosis (DVT) is echo-Doppler examination with compression ultrasonography (CUS). Peripheral arterial and venous evaluation with Doppler ultrasound is a low-cost, noninvasive technique that can be performed quickly and easily at bedside. This imaging technique can be also applied to control the patency of indwelling cannula and the presence of superimposed thrombosis or infection. Silent pulmonary embolism may be uncovered during imaging exams for cancer staging.

Peripheral Vascular Disease

Peripheral artery disease (PAD) can have different clinical presentations and etiologies. The early presentation can be Raynaud's with a broad degree of vasospasm and even ischemic fingertip necrosis [8]. It is usually associated with cancer drugs such as bleomycin, vinca alkaloids, cisplatin, carboplatin, gemcitabine, and IFN-alpha treatments [9–12]. PAD of the lower extremities has a prevalence of about 30% in cancer patients undergoing treatment with nilotinib, ponatinib, or BCR-ABL tyrosine kinase inhibitors (mainly used in myeloid leukemia) even in patients with no concomitant cardiovascular risk factors [13]. PAD evolution is characterized by rapidly progressive atherosclerosis, vessel occlusions, and formation of collateral circulation. PAD can occur

in the first month of chemotherapy treatment (rapid onset) or several years after its completion (late onset). Among other antineoplastic treatments, peripheral vascular disease can be associated with assumption of L-aparaginase, methotrexate, 5-fluorouracile, and paclitaxel [14]. Renal and visceral arteries can be involved resulting in acute ischemic events in different organs [15–20]. Of interest, in several cases, PAD progression keeps its course despite chemotherapy discontinuation and optimal medical management [21–23], demonstrating that the mechanism of progression of this disease is still unclear. Chemotherapy-induced PAD can affect also big vessels because of increased arterial stiffness. Anthracyclines can increase aortic wall stiffness 3 months after treatment, as demonstrated by using cardiac magnetic resonance (CMR). The increment in aortic stiffness seems to occur soon after the chemotherapy infusion and is dose independent. Abnormal increment of aortic stiffness showed to be associated with left ventricular (LV) hypertrophy and exercise intolerance and predicts future cardiovascular events [24, 25].

The main strategy of prevention corresponds to an appropriate risk identification of developing PAD before the beginning of anticancer therapy. The risk assessment for PAD involves mainly the identification of traditional cardiovascular risk factors (diabetes mellitus, arterial hypertension, smoke habits, dyslipidemia, obesity, and family history of premature coronary artery disease, sedentary lifestyle) and of the presence of clinical symptoms suggestive of claudication (i.e., Edinburgh questionnaire) and complete physical examination including check of peripheral pulses and the ankle-brachial index (ABI) measurement [26].

Modifiable risk factor control should be corrected before starting the treatment with drugs at vasotoxic risk, and periodic controls of blood pressure, lipids, and blood glucose are recommended [27]. In the suspicion of PAD, further investigation such as peripheral arteries ultrasound should be performed. In case of clinical severe PAD manifestations, the therapeutic strategy should be discussed among multiple clinicians, including oncologists/hematologists, cardiologists, and vascular surgeons, to identify individual risks and forecast the benefit of eventual percutaneous or chirurgical revascularization [28].

Stroke

Cancer patients are at higher risk of cerebral thromboembolic event including those related to paradoxical embolization of indwelling catheters [29–31]. Although hypercoagulability may play a relevant role, some anticancer agents may upraise the risk of stroke (5-fluorouracil, cisplatin) [31–36]. Treatment with tyrosine kinase inhibitors (particularly BCR-ABL TKI such as nilotinib and ponatinib) has been found to be related with a high risk of stroke caused by a rapid progression of carotid artery occlusion (50–60% to subtotal occlusion in 1 year) [37]. The incidence of stroke is at least doubled in patients after mediastinal, cervical, or cranial radiotherapy [38]. The main physiopathology mechanism that could cause ischemic event in small vessels is represented by direct endothelial damage and thrombus formation. In larger vessels, the production of ischemic events is based on three main mechanisms: (i) vasa vasorum occlusion and concomitant necrosis of the medial layer, (ii) adventitial fibrosis causing increased carotid stiffness and intima thickness, and (iii) accelerated and advanced atherosclerosis [39].

Also in this setting, the correction of cardiovascular risk factors is necessary to reduce the risk of atherosclerotic progression. In patients undergoing mediastinal, cervical, or cranial radiotherapy cerebrovascular ultrasound screening is recommended. Ultrasound screening is suggested after the first 5 years of irradiation and every 5 years. If significant lesions or symptoms are detected during the follow-up, early and more frequent control are mandatory. Carotid arteries ultrasound should be considered also in patients undergoing drugs at high vasotoxic risk. A 12-lead ECG is also recommended to identify atrial fibrillation, a recognized determinant of stroke. A complete echocardiographic exam is also indicated to rule out other possible sources of embolism such as foramen ovale, heart valve

diseases, regional wall motion abnormalities consistent with CAD, and LV aneurysms [40]. Cerebrovascular imaging should be performed at onset of suspected neurological manifestation as recommended by published guidelines [41].

Coronary Artery Disease

Myocardial ischemia may occur as a consequence of several anticancer therapies through different mechanisms. It can be in fact the result of direct endothelial injury (cisplatin [42]), 5-fluorouracil, [43] vasospastic effect (VEGF inhibitors [44]), acute arterial thrombosis (tyrosine kinase inhibitors [31]), or long-term accelerated atherosclerotic process. Radiotherapy is associated with an elevated incidence of CAD, whose mechanism includes premature atherosclerotic processes and coronary vasospasm [45–50]. Radiotherapy-induced coronary lesions are usually ostial (left anterior descending artery is mainly affected during breast cancer irradiation of the left hemithorax) and potentially may induce life-threatening complication.

CAD can present atypical clinical manifestations or develop asymptomatically (silent myocardial ischemia), with a prevalence which appears to be higher in comparison with the general population, [51, 52] likely because of concomitant neurotoxicity due to radio- and chemotherapy. Obviously, a pre-existing CAD significantly increases the risk of anticancer therapy-related CAD [53]. Consequently, identification of CAD before initiating cancer treatments is crucial, and echocardiography plays a pivotal role in the diagnostic work-up in this subset of patients, through the identification of regional wall motion abnormalities. Coronary arteries may be affected by accelerated atherosclerosis especially in patients undergoing anthracycline chemotherapy [54–56]. A high calcium score has been found after mediastinal radiation (>20 Gray) [57, 58]. Nevertheless, in absence of symptomatic CAD, there is no evidence about the advantage of performing a routine CT angiography or calcium scoring after high-dose radiation therapy [59]. It is also worthy of note that baseline (before the beginning of anticancer therapy) calcium score does not predict cardiovascular events in cancer patients undergoing subsequent anticancer therapy, including classic chemotherapy as well as tyrosine kinase inhibitors or radiotherapy.

Measurement of Preclinical Vascular Damage

In patients undergoing vasotoxic antineoplastic drugs, it is particularly important to early detect preclinical atherosclerosis, for a more accurate cardiovascular risk stratification and thus for early starting protective therapies such as aspirin and statins. According to some authors, the risk to develop thrombotic complications, in patients undergoing some vasotoxic drugs such as ponatinib, is so high that treatment with aspirin may be considered in primary prevention even in low-risk patients [60].

Carotid ultrasound can be used to refine cardiovascular risk stratification, focusing on the measurement of the intima-media thickness (IMT) and the presence and characteristics of plaques (Fig. 18.1).

An increased IMT (>0.9 mm) and more consistently the presence of plaque (focal wall thickening >1.5 mm) are associated with increased risk of stroke and cardiac events [61, 62]. Particularly echolucent plaque, with respect to calcified one, seems to confer a higher risk of cerebrovascular events [62]. However, a recent meta-analysis failed to demonstrate a higher predictive value of IMT compared to the Framingham risk score in predicting future cardiovascular events, even in the group of patients at intermediate risk; for this reason, the recent guidelines of the European Society of Cardiology on cardiovascular prevention suggest only carotid artery plaque assessment as a modifier in CV risk prediction, in patients at intermediate risk [63].

Another early marker of vascular damage is measurement of arterial stiffness. It measures vascular elasticity, and thus it is a functional marker of damage and for this reason more precocious than even IMT. The most commonly

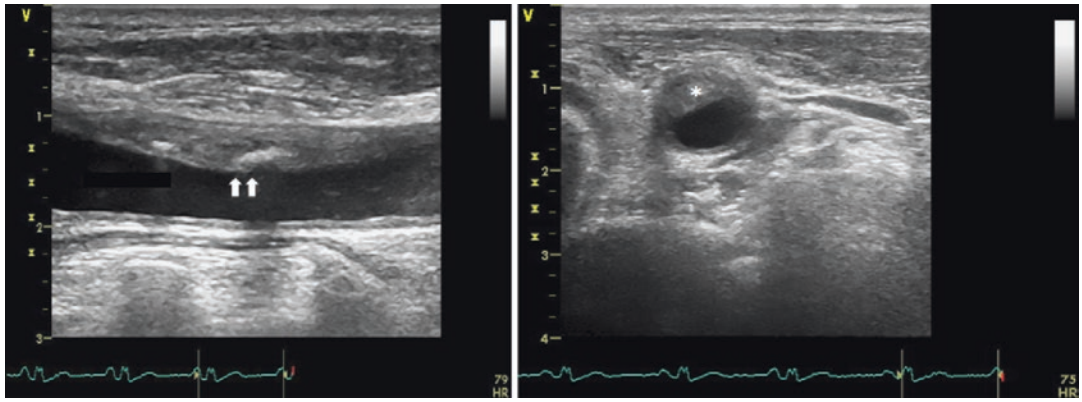

Fig. 18.1 Carotid plaque detected by carotid ultrasound

measured parameter is pulse wave velocity (PWV) or arterial augmentation index. An increased arterial stiffness predicts future CVD and improves risk classification [64]. Therefore, it may be used in patients close to the threshold to improve risk stratification [63].

The assessment of the endothelial function may be useful to detect very precocious alteration of vasculature. Brachial artery flow-mediated dilation (FMD) is the most diffuse technique capable of assessing endothelial function. FMD is a noninvasive test based on the ultrasound evaluation of peripheral arterial response to an increased share stress. It correlates with invasive testing of coronary endothelial function, as well as with severity and extent of coronary atherosclerosis [65].

Another easy and not invasive method to early detect the presence of peripheral atherosclerosis in asymptomatic individuals is ABI. This index indicates the presence of significant peripheral arteries atherosclerosis (≥50%) when <0.9 [66, 67] and inversely correlate with cardiovascular risk.

Some patients may undergo provocation testing with cold stress, particularly when anticancer treatment such anti-VEGF antibody is indicated, due to its effect on lower endothelial NO level.

Coronary artery calcium (CAC) is also a noninvasive imaging technique that may be considered as a risk modifier in CV risk assessment; it is measured through electron beam or multislice CT [63]. The most used parameter to quantify the extension of calcifications is Agatston score. It has been showed that the extent of coronary calcifications correlates with the extent of total coronary plaque burden, but it does not correlate with plaque instability [68]. This test has a particularly high negative predictive value.

In the suspicion of coronary artery disease, another test to be performed is stress echo, and this will be treated into a dedicated chapter (Chap. 17).

Imaging Study for Follow-Up Evaluation

There is no commonly established timing for the surveillance of cardiovascular manifestations, because of discrepancies in expert opinions and absence of clear suggestions from official guidelines [69]. Figure 18.2 is an algorithm proposed to summarize the main expert opinions of oncologist and cardiologic recommendations. Based on these assumptions, some suggestions could be recommended:

(i) Annual follow-up and physical examination, including both serial ECG and test to study cardiac function, for patients with history of high-dose mediastinal radiation exposure (≥20 Gray) and cardiotoxic chemotherapy (i.e., cumulative dose of anthracyclines ≥300 mg/m^2) or for those who underwent combined chemo- and radiotherapy.

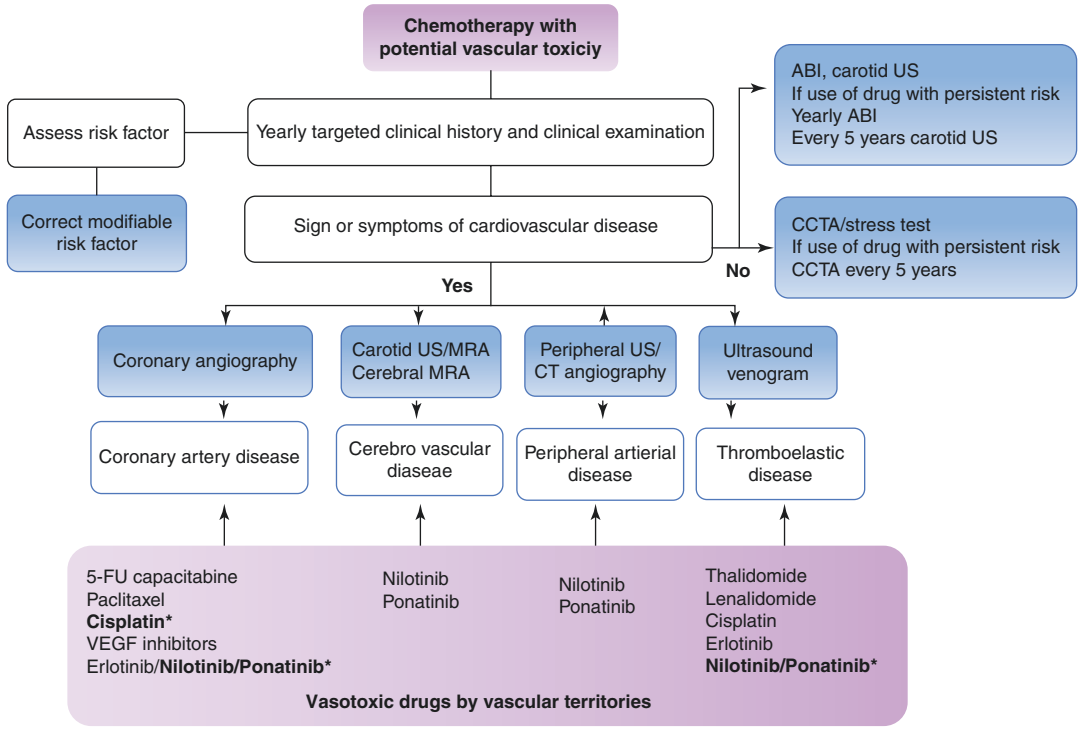

Fig. 18.2 Suggested algorithm for cardiovascular screening of cancer patients who undergo chemo- and/or radiotherapy. ***Bold drug*** with persistent risk even after therapy. ABI, ankle-brachial index; CCTA, cardiac computed tomography angiography; US, ultrasound

(ii) For lower-risk patients, cardiology evaluation with serial ECG every 2–5 years [70].

(iii) Functional stress echocardiography every 5–10 years in patients following radiation exposure to the heart, along with risk factor modifications [53].

(iv) Screening for carotid artery disease by carotid ultrasound, beginning the first exam 5 years after supraclavicular radiation treatment and repeating it every 5 years. Shorter follow-up (every 2 years) should be performed in older (>60 years old) or in symptomatic patients, in those with well-established carotid artery disease, and in those whose ongoing treatment is considered at high vascular toxic risk; screening carotid artery ultrasound should be considered also in patients undergoing strongly vasotoxic drugs, such as ponatinib and nilotinib.

(v) Subclavian arterial ultrasound in patients who received radiation of the head and neck.

(vi) Renal artery echo-Doppler exam in symptomatic patients who received abdominal and pelvic radiation.

(vii) Lower extremity ultrasound exam and ankle-brachial index (ABI) evaluation in symptomatic patients or in those who received potential radiotherapy with lower extremity exposure.

Conclusions

Vascular adverse effects such as ischemia, thromboembolism, and arterial hypertension are commonly associated with several anticancer therapies. Mechanisms of vascular toxicity of such agents are thought to involve either direct damage of endothelial tissue or induction of endothelial dysfunction due to inhibition of vascular relaxation. Accordingly, promptly detection of these possible adverse effects by vascular imaging should be strongly promoted to introduce efficient prophylactic therapies when indicated. It is fundamental to

diagnose vascular complications and treat them aggressively in order to reduce deleterious adverse effects of anticancer therapy.

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Prevention and Clinical Management of Cardiovascular Damage Induced by Anticancer Drugs: Need for Early Biomarkers and Cardio- and Vasculoprotection in Personalized Therapy

Rosalinda Madonna, Francesca Macaione, and Peter Ferdinandy

Introduction

Improvements in early cancer diagnosis and advances in therapeutic approaches have led to a significant decrease in cancer mortality in the past two decades [1]. To achieve these results, however, a considerable price has been paid in terms of cardiovascular adverse side effects in patients treated with traditional agents (i.e., anthracyclines and cyclophosphamide), as well as new agents (monoclonal antibodies and tyrosine kinase inhibitors) [2, 3]. The phenomenon is expected to rise, because of the increasing number of patients undergoing anticancer therapy and their improved life expectancy enough to allow these effects to manifest and become the prime concern [4]. As a result, there has been a surge of interest to prevent and mitigate adverse sequelae of cancer therapy. The spectrum of cardiovascular complications of cancer therapy, induced both by old and new agents, includes left ventricular (LV) dysfunction (LVD) and heart failure (HF) [5], treatment-induced hypertension, vasospastic and thromboembolic ischemia, acute coronary syndromes, and arrhythmias [6, 7]. More in detail the term of cardiovascular damage generally includes two types of damage closely related to each other: the cardiac toxicity and vascular toxicity induced by antineoplastic drugs.

The most common form of antineoplastic drug-induced cardiotoxicity is left the LVD which may be subclinical (or asymptomatic), but may also progress until congestive HF, and ultimately to death. The development of LVD induced by antineoplastic drugs, in particular by traditional agents (anthracyclines, cyclophosphamide, 5-fluorouracil, docetaxel, and paclitaxel) but also, unexpectedly, new agents, such as monoclonal antibodies (trastuzumab) and tyrosine kinase inhibitors (TKI) (imatinib, dasatinib, nilotinib, sunitinib, sorafenib, and bevacizumab), has been extensively studied [8]. In contrast, vascular toxicity induced by anticancer drugs is

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poorly analyzed, yet it can be responsible for increased morbidity and/or mortality, thus limiting effectiveness of cancer therapies.

To date it is known that vascular endothelium plays a fundamental role in the maintenance of tissue homeostasis. It is also known that a healthy endothelium is essential for the homeostasis of the whole cardiovascular system. In maintaining vascular homeostasis, vascular endothelial growth factor (VEGF) plays a key role by the production of the vasodilator nitric oxide (NO) and decreased vascular resistance through the generation of new blood vessels [9]. The recent use of tyrosine kinase inhibitor (i.e., sunitinib) mainly for the treatment of renal cell carcinoma has determined an increased incidence of heart failure through mitochondrial injury and cardiomyocyte apoptosis [10, 11], as well as vascular toxicity. The vascular toxicity of chemotherapy often reflects endothelial dysfunction, with loss of vasorelaxant effects and suppressed anti-inflammatory and vascular reparative functions. Therefore, it is not surprising that antiangiogenic drugs targeting VEGF (e.g., by bevacizumab, aflibercept, sorafenib, sunitinib, pazopanib, vandetanib, axitinib, regorafenib, or cabozantinib) not only efficiently act against tumor growth but may also induce endothelial dysfunction with increased risk of arterial thromboembolic and, especially, hypertension [12]. It follows that maintaining endothelial function during or following treatments with antineoplastic drugs, without affecting antitumor drug effectiveness, is essential for preserving or recovering cardiovascular homeostasis.

These observations suggest that the best treatment for chemotherapy-induced cardiovascular toxicity is its prevention in patients with high risk of developing cardiovascular toxicity. Currently, several preventive measures are being used, including a correct assessment of the cardiovascular risk factor prior and during treatment with anticancer drugs; close monitoring of cardiovascular cardiac function; limiting cumulative chemotherapy dose; promoting, in high-risk patients selected by means of biomarkers, a positive health behavior (healthy diet, smoking cessation, regular exercise, weight control); and planning cardiovascular protectants to the antineoplastic regimen and pharmacologic therapies including ACEi, beta-blockers, statins, nitric oxide donors, and/or antioxidant strategies that might prevent and/or therapeutically control cardiotoxic effects in cancer patients improving the cardiac and endothelial function.

Optimal strategies for the diagnosis, surveillance, and management of cardiovascular complications in patients who receive chemotherapy agents remain incompletely defined and can be challenging.

In general terms, all patients receiving cardiovascular toxic chemotherapy should undergo a cardiovascular assessment, including cardiovascular biomarkers (i.e., troponins and natriuretic peptides) and LV function evaluation, during follow-up and after treatment completion [13–15].

In the last years, the identification of new genes and signaling pathways by the "omics" approaches in clinical practice could allow us to arrange preventive interventions and personalize cancer therapy in the era of individualized patient care.

In this chapter, we provide an overview of cardioprotection and vasculoprotection in the setting of cardiovascular damage, outlining the state of the art in the clinical management of cardiovascular damage. We discuss the potential clinical utility of "omics" approaches for the early detection and prediction of cardiovascular damage and individual responses to antineoplastic drugs.

Treatment of Chemotherapy-Induced Cardiovascular Damage: Recent Clinical Trials

The development of cardiovascular damage during or after anticancer therapy administration represents a growing problem. At present, no clear guidelines for the treatment of anticancer-induced cardiovascular damage are available yet.

Regarding the cardiotoxicity, existing recommendations focus mainly on continuation/withdrawal/resumption of anticancer therapy, according to LV ejection fraction (EF) values [3, 8, 13].

In this context, recent studies have evaluated the role of standard HF therapies [16–19].

In patients treated with anticancer drugs, cardioprotective effects have been shown for dexrazoxane, beta-blockers (carvedilol, nebivolol), angiotensin-converting enzyme inhibitors (enalapril), angiotensin receptor blockers (valsartan, telmisartan), spironolactone, and statins (atorvastatin), which act at various molecular and cellular levels [20–22].

Regarding the vascular toxicity induced by anticancer treatment, different classes of drugs especially with antioxidant properties have been shown to improve endothelial function and in some instances to reduce the risk of cardiovascular diseases associated with treatment with chemotherapeutic agents.

Among them, angiotensin-converting enzyme inhibitors (ACEi), antioxidants, and statins have direct effects on cardiac endothelial cells, while angiotensin receptor blockers (ARBs), renin inhibitors, beta-blockers, and estrogens indirectly affect endothelial cell function. All these drugs have in common the ability to upregulate the eNOS pathway leading to an increase in plasma NO availability and a general improvement of endothelial function.

ACE Inhibition and Angiotensin II Receptor Antagonists

ACE-Is and ARBs have a key role in modulating chemotherapy-induced cardiotoxicity exerting positive effects in reducing the progression of LV dysfunction and in preventing HF in asymptomatic high-risk patients [18]. The rationale for using renin-angiotensin-aldosterone system (RAAS) blockade drugs is not simply related to hemodynamic effects due to reduced AngII production, like reductions in post-load and persistent mitigation of sympathetic tone [23], but also to direct anti-remodeling and antioxidant properties including a reduction in interstitial fibrosis [24], attenuation of oxidative stress [25], improved intracellular calcium handling [26], and alterations in gene expression that affect cardiomyocyte metabolism and mitochondrial function [27] which rate this class of drugs as a first-line HF therapy [28, 29].

ACEi, like enalapril or captopril, have a pivotal role in the specific treatment of anthracycline-induced cardiac injury even if they are administered after anthracyclines, cardiomyocyte necrosis, and increase of circulating troponin [28]. In a study of 115 patients treated with ANTs, enalapril was shown to significantly reduce the incidence of LV dysfunction in comparison with a placebo [30]. The temporal indication is that ACEi treatment should be started as soon as possible after completing chemotherapy [30]. Indeed, no response was observed in patients in whom therapy was initiated >6 months after completion of chemotherapy [16].

The OVERCOME trial has evaluated the efficacy of enalapril in association with carvedilol in preventing the reduction of FE in patients with hematologic diseases treated with anthracyclines. After 6 months, LVEF did not change in the treated group but significantly decreased in untreted group. The treated patients also exhibited lower incidence of cardiac events, death, and decompensation [31].

The ACEi due to their multiple potential action mechanisms could be used to cardiac repair with any type of anticancer drugs. However the treatment of trastuzumab-related cardiotoxicity (TIC) is a more controversial issue; in fact this is an area of current active investigation.

No evidence-based recommendations for the treatment of patients developing cardiac dysfunction after trastuzumab therapy have been proposed. The evidence that supports the use of ACEi in this setting is limited to case series. Despite evidence, the potential efficacy of ACEi in improving LVEF in patients receiving trastuzumab remains uncertain. In trastuzumab-treated patients, the ACEi cardioprotective effect may be due to the fact that angiotensin is a potent downregulator of the NRG-1/ErbB system, so the inhibition of the ACE system could have a positive effect.

Regarding the vascular toxicity, multiple investigative and clinical observations have demonstrated that hypertension is the most common chemotherapy-induced vascular damage resulting

from treatment with VEGF inhibitors. The rates of hypertension appear to depend on the antiangiogenic agent used, the tumor type, and patient-related factors including age and comorbidity. Angiogenesis inhibitor-related hypertension is typically manageable with early initiation of pharmacologic therapy to reach accepted blood pressure (BP) targets [8]. Preferred antihypertensive agents for angiogenesis inhibitor-associated hypertension include ACEi and dihydropyridine calcium channel blockers; although there are minimal data to suggest superiority of a single class of agents, the ACEi have showed vasculoprotective properties related to multiple mechanisms as activation of eNOS (dependent on its turn from bradykinin improved half-life), stimulation of protective intracellular signaling and metabolic pathway, and antioxidant and ROS scavenger properties.

In particular among the ACEi, zofenopril seems to have an important role in the treatment of vascular toxicity. Zofenopril through its sulfhydryl group (−SH) exhibits both potent antioxidant and scavenger effects and anti-inflammatory action [32] promoting endothelial cell survival [33]. In microvascular endothelium, zofenopril upregulates eNOS, FGF-2, and telomerase (TERT) mRNA, inducing cell survival, rescuing damaged endothelial cells (EC), and promoting physiological angiogenesis without synergistic effects with known angiogenic factors produced by tumors as VEGF [33, 34].

Moreover the ACEi zofenopril preserves coronary EC survival and function damaged by doxorubicin and appears to exert its protective effects owing to its SH group, besides the ACE inhibitory function [35, 36].

There are few studies on cardioprotective vasculoprotective action of ACEi in patients treated with tyrosine kinase inhibitor and target drugs.

It is known that at the base of cardiotoxicity from sunitinib, there is an energy imbalance, so agents that improve myocardial energy intake and the activity of adenosine monophosphate-activated protein kinase (AMPK) may be beneficial.

ACEIs such as the beta-blockers may improve myocardial energy intake, and this may explain their cardioprotective effect in association with these target drugs [37].

Candesartan has been shown to treat experimental cardiotoxicity already induced by anthracycline [38], whereas pre- and posttreatment with telmisartan protected against acute doxorubicin-induced cardiotoxicity in rats [39]. Telmisartan is the only ARB-modulating peroxisome proliferator-activated receptor-c (PPAR-c), therefore affecting the bioavailability of NO and inhibiting inflammatory molecules such as interleukin 6 (IL-6) and tumor necrosis factor (TNF) [40].

The cardioprotective role of telmisartan was evaluated in patients treated with epirubicin. In this small prospective study, the patients who started telmisartan a week before of chemotherapy did not show a significant reduction in myocardial deformation indices and a significant increase in ROS or interleukin respect the patients of the placebo arm that had a significant IL-6 and ROS increase [41]. These results suggest that telmisartan might protect against epirubicin-induced ROS production and inhibit the generation of inflammation, thus preventing the development of early myocardial impairment [41].

PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) [42] evaluated the role of candesartan and metoprolol in preventing the development of heart failure in patients treated with epirubicin with or without trastuzumab. In this study the candesartan but not metoprolol protected the heart against early FE decline evaluated by cardiac magnetic resonance. In another study, Nakame et al. who designed to characterize acute CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)-induced cardiotoxicity in patients with non-Hodgkin's lymphoma demonstrated that the valsartan showed a cardioprotective effect on acute cardiotoxicity in patients treated with high doses of ANTs [43]. In this study the patients treated with valsartan did not present more frequently preserved LVEF, but it significantly inhibited ventricular dilatation, elevation of natriuretic peptides, and prolongation of the QTc interval.

Many other ongoing clinical trials are evaluating the role of ACE-Is and ARBs as cardiopreventive

agents that may act by decreasing angiotensin-induced blockade of the neuregulin 1/ErbB pathway.

Finally, meta-analysis and retrospective studies on cancer patients treated with anthracyclines, trastuzumab, and tyrosine kinase inhibitors who had developed a drop in LVEF showed that cardioprotective interventions with ACEi and ARBs lead to recovery of myocardial function and reduction of cardiac events, thus allowing patients to complete cancer therapy [44, 45].

To date, however, cardioprotective treatment with ACE-Is or ARBs still requires convincing evidence from large randomized and prospective trials.

β-Blockers

Although the exact mechanisms of cardioprotection and vasculoprotection with β-blockers remain to be delineated, the β-adrenergic inhibitors are able to diminish mortality in patients with systolic heart failure, and there is currently an increased use of these agents to decrease the range of cardiotoxic effects induced by chemotherapy [46]. Certain β-blockers (carvedilol, nebivolol, alprenolol) inhibit β-adrenergic receptor-mediated G protein-coupled receptor signaling while preserving β-adrenergic receptor recruitment of β-arrestin and transactivation of ErbB1 (or epidermal growth factor receptor) [47, 48]. Beta-arrestin is cardioprotective under long-term catecholamine stimulation, and activation of pro-survival signaling via the ErbB receptor pathway and related downstream mediators has been associated with an attenuation of anthracycline-induced cardiotoxicity.

Carvedilol, specifically, a nonselective β and α1 adrenergic antagonist with antioxidant properties, has also been shown to reduce anthracycline-induced cardiovascular toxicity. Carvedilol protects cells against doxorubicin toxicity by reducing oxidative stress and apoptosis [49, 50].

Studies in animal models have shown that carvedilol mitigates oxidative stress in a variety of pathologic states including ischemia-reperfusion injury [51] and dilated cardiomyopathy [52]. This antioxidant activity of carvedilol, rather than its β-blocking action, seems to be responsible for its cardioprotective effects.

A study comparing carvedilol to atenolol, a β1-selective antagonist without antioxidant properties, showed that carvedilol, but not atenolol, prevented mitochondrial damage and reduced the histopathologic changes associated with doxorubicin cardiotoxicity [53].

As known the anthracycline therapy may lead to impaired diastolic relaxation via titin proteolysis and impaired intracellular calcium sequestration [54]. β-Blockade prevents myocardial calcium overload and results in enhanced lusitropy [55], providing further potential mechanistic rationale toward the favorable effects of this therapy. In a small, randomized placebo-controlled study, patients treated with carvedilol at anthracycline initiation showed attenuation of the decline in LVEF observed in the placebo group at 6 months [56] and attenuated alterations in diastolic function.

Recent data from the OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and caRvediolol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) trial have also shown that β-blocker therapy, in combination with angiotensin-converting enzyme (ACE) inhibitor therapy, may be beneficial in preventing anthracycline-induced cardiotoxicity, with treated patients demonstrating less significant changes in LVEF and a lower incidence of death or HF compared with placebo [31]. Other recent data from the PRADA (PRevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy) study have shown that the beta-blockade may attenuate early myocardial injury in patients with early breast cancer undergoing anthracycline, but whether this attenuation translates into reduced risk of developing ventricular dysfunction in the long-term remains unclear [57].

In the last years, a cardioprotective and vasculoprotective role against antineoplastic drugs cardiotoxicity has been showed by nebivolol. This third-generation beta-blocker is a highly selective β1-blocking agent which has additional

cardioprotective and vasculoprotective properties via peripheral vasodilation mediated by the nitric oxide pathway [58]. It also provides antioxidant characteristics [59, 60]. De Nigris et al. demonstrated a reduction in cardiac toxicity in rat hearts that were exposed to anthracycline [61]. A human study demonstrated prophylactic use of nebivolol against anthracycline-induced cardiotoxicity in patients with breast cancer receiving anthracycline (patients treated with nebivolol did not show any change in FE or increased BNP after 6 months) [62].

Beta-blockers that increase ERK activation through beta-arrester (nebivolol and carvedilol) may play a role in treating dysfunction from sorafenib [48]. Few studies evaluated the cardioprotective and vasculoprotective action of beta-blockers in patients treated with trastuzumab therapy and tyrosine kinase inhibitor.

Impaired myocardial energetics may contribute to sunitinib-induced cardiac dysfunction, generating the hypothesis that agents that promote favorable myocardial energetics could be beneficial. The introduction of a constitutively active AMPK into cardiomyocytes resulted in partial resistance of these cells to sunitinib-induced apoptosis [63] suggesting that agents that augment AMPK activity may attenuate sunitinib-induced cardiotoxicity. Conventional therapies for HF—ACE inhibitors and β-blockers— have been shown to improve myocardial energetics as part of their cardioprotective effects [37, 64].

Nonrandomized data suggest that the combination of ACE inhibitors and carvedilol is beneficial for the recovery of LVEF in patients treated with trastuzumab after initially experiencing cardiotoxicity with this agent [65]. In a retrospective study of patients treated with trastuzumab, dual therapy with ACE inhibitors and β-blockers was associated with LVEF recovery at 12 months [66]. However, large, placebo-controlled randomized clinical trials are warranted to determine the timing of initiation of these medications and the patients most likely to benefit from their use.

There are a number of ongoing studies investigating the opportunity of using β-blockers in the prevention of cardiovascular toxicity induced by trastuzumab including multidisciplinary approach to new therapies in Cardiology Oncology Research Trial [67] and NCT0100818 (http://www.clinicaltrials.gov).

Mineralocorticoid Receptor Antagonists

Aldosterone antagonism has been evaluated in a very recent trial that included 83 patients with breast cancer who were randomized to spironolactone or placebo and a concomitant anthracycline-containing chemotherapy control groups [68]. In this study Akpek et al. showed that during at least 24 weeks of treatment, including 3 weeks after completing anthracycline-containing chemotherapy, spironolactone protects both myocardial systolic and diastolic functions [68]. Therefore spironolactone could be used to protect against anthracycline-induced cardiotoxicity.

Mineralocorticoid receptor antagonists are increasingly being used to treat resistant hypertension [69] and might therefore have a vasculoprotective role in the management of VEGF inhibitor-associated hypertension.

Dihydropyridine Calcium Channel Antagonists and Thiazide Diuretics

As discussed previously, hypertension is the most common chemotherapy-induced vascular damage resulting from treatment with VEGF inhibitors. Dihydropyridine calcium channel antagonists and thiazide diuretics as well as mineralocorticoid receptor antagonists and β-blockers may be used if additional antihypertensive agents are required [69, 70].

Nondihydropyridine calcium channel antagonists, such as verapamil or diltiazem, should be avoided because these agents inhibit cytochrome P450 3A4, through which VEGFIs, such as sorafenib and sunitinib, are metabolized. Therefore the co-prescription of nondihydropyridine calcium channel blockers can provoke increased plasma antiangiogenic drug concentrations [71].

Statins

Oxidative stress is a key component in linking environmental toxicity to the multistage carcinogenic process.

Statins are known to have pleiotropic effects including antioxidant and anti-inflammatory properties. Statins, in fact, decrease oxidative damage by stabilizing mitochondria and decreasing vascular inflammation [72, 73].

In an animal model, it was demonstrated that pretreatment with fluvastatin blunted anthracycline-induced toxicity, reducing oxidative stress, enhancing the expression of antioxidative enzyme mitochondrial superoxide-dismutase-2, and limiting cardiac inflammation [74].

Only small clinical studies have evaluated the effects of statins in patients treated with anthracycline, [75, 76] reporting only minor positive results.

In a retrospective cohort study of 628 breast cancer patients treated with trastuzumab, uninterrupted statin therapy had a cardioprotective effect against heart failure [75]. In a randomized control trial of 40 patients treated with doxorubicin, prophylactic atorvastatin was effective in maintaining LVEF compared to placebo [77]. Larger studies are necessary to confirm the efficacy of statins in counting the cardiovascular toxicity related to anticancer drugs [44, 75, 77, 78].

Nonpharmacologic Strategies: The Role of Dietary and Aerobic Exercise

The cardiovascular toxic mechanisms involving oxidative stress provide the rationale for using nutritional supplementation and exercise training that may have important antioxidant properties. Dietary supplementation of antioxidants proved to be able to alleviate doxorubicin cardiovascular toxicity in animal models [79], but clinical data are necessary to confirm its efficacy in counting cancer therapy-related vascular toxicity and cardiotoxicity [80].

To date the aerobic exercise is considered as a promising nonpharmacological strategy to prevent and/or treat chemotherapy [81]-induced cardiovascular toxicity [82]. In fact aerobic exercise is associated with numerous beneficial effects on the endothelium and on cardiovascular risk factors, and may potentially modulate some of the mechanisms of vascular damage associated with antineoplastic therapies, thereby reducing their cardiovascular toxicity [83]. It has been speculated that aerobic exercise can decrease ROS generation, inhibiting proapoptotic signaling, restoring proper calcium cycling, and stimulating the AMPK pathway, thus improving myocardial energetics [84]. In addition, exercise can have a positive impact on CV risk factors, such as hypertension, high cholesterol and lipids, overweight and obesity, and high blood glucose or diabetes [85].

In cancer survivors, a short period of mixed aerobic and resistance exercise builds tolerance and flexibility in physical activity [86]. Although several studies have shown a role of aerobic exercise as promising strategy to prevent anthracycline- [87] and trastuzumab-related [88] cardiovascular toxicity, further mechanistic, translational, and clinical research are needed to investigate the potential protective role of exercise on the vascular toxicity of cancer treatments [89].

Prevention of Chemotherapy-Induced Cardiovascular Damage

The best treatment of cancer drug-induced cardiovascular toxicity is its prevention. The prevention may be extended to all patients before chemotherapy administration (primary prevention) or may be addressed in selected high-risk patients, showing preclinical or initial signs of cardiotoxicity (secondary prevention), in order to promptly start a treatment against progression to overt HF [90].

In context of the prevention, a close collaboration between oncologists and cardiologists is needed. In this emerging interdisciplinary alliance, in particular the cardiologists should pay attention to several aspects to reduce both the burden of potential cardiovascular complications and the number of patients disqualified from specific cancer treatment because of emergent CVD [91, 92].

These aspects include a careful initial evaluation before starting potentially cardiotoxic chemotherapy, an optimal control of preexisting cardiovascular risk factors, and a careful monitoring during the treatment to individuate the early signs of cardiovascular toxicity and readily implement preventive or therapeutic measures [93, 94].

For the primary prevention, the first step is the identification and correction of preexistent cardiovascular risk factors and the therapy-related risk factors for chemotherapy-induced cardiotoxic events in all patients proposed for anticancer treatment.

It is known that the incidence of chemotherapy-induced cardiovascular toxicity is variable, and the patient-related risk factors so far described are age, female gender, history of or preexisting cardiovascular disorders, electrolyte imbalances such as hypokalemia and hypomagnesemia, concurrent administration of cardiotoxic agents, and prior anthracycline chemotherapy or prior mediastinal radiation therapy [95], and the therapy-related risk factors for chemotherapy-induced cardiotoxic events include drug type, total dose administered during a day or a cycle, cumulative dose, administration schedule, route of administration, association with other cardiotoxic drugs, or concomitant radiotherapy [95].

Although, at present, recommendations for screening and monitoring of these patients are lacking, there is some evidence showing that a good control of common cardiovascular risk factors at initiation of chemotherapy mitigates the cardiovascular consequences of cancer treatment in patients with a history of hypertension, diabetes, and HF [96, 97].

In the primary prevention, therefore, a control of preexisting risk factors such as blood pressure, glucose, and cholesterol levels is essential, and positive health-promoting behavior, including lifestyle factors (healthy diet, smoking cessation, regular exercise, weight control), should be strongly advised. In particular, aerobic exercise is considered as a promising nonpharmacological strategy to prevent and/or treat chemotherapy-induced cardiovascular toxicity [81].

As emerged by the previous paragraph, adding cardioprotective agents to anticancer drugs is another strategy of primary prevention. In the setting of the cardioprotective dexrazoxane has an important role. Dexrazoxane is the only drug approved by the US Food and Drug Administration for the prevention of cardiotoxicity induced by anthracycline treatment in adults. This drug acts by chelation of iron redox-active molecules, thus preventing the formation of anthracycline-iron complex and subsequent development of reactive oxygen species [98]. Since the use of dexrazoxane implies additional costs and some uncertainties, therefore the American Society of Clinical Oncology (ASCO) guidelines say it can be considered for patients with metastatic neoplasm, already treated with a cumulative doses of doxorubicin >300 mg/m2, and that may benefit from further anthracycline administration [99].

The use of cardiovascular drugs as cardioprotective and vasculoprotective agents as a primary prevention strategy has been evaluated, but its utility in clinical practice. In this context, as mentioned in the previous paragraph, beta-blockers [62, 100], angiotensin antagonists [41, 43], aldosterone antagonists [68], and statins [75–77] have been demonstrated to exert a cardioprotective and vasculoprotective. Among ongoing trials, the SAFE trial (Cardiotoxicity Prevention in Breast Cancer Patients Treated with AC and/or trastuzumab) is evaluating whether the use of ramipril or bisoprolol or their combination can prevent heart failure development in women receiving neo-adjuvant or adjuvant anthracycline-containing chemotherapy, with or without trastuzumab (NCT02236806). Other proposed cardioprotective agents include coenzyme Q10, carnitine, n-acetylcysteine, the antioxidant vitamins E and C, the erythropoietin, the endothelin-1 receptor antagonist bosentan, and the lipid-lowering agent probucol, as demonstrated by preliminary experimental observations. However, their efficacy in preventing cardiovascular toxicity prevention is unknown and needs further investigation [90].

Finally, as part of the primary prevention, a multinational, multicenter, randomized controlled clinical trial is ongoing to determine whether using changes in global longitudinal strain (GLS) to guide the initiation of cardioprotective therapy

in patients receiving cardiotoxic chemotherapy improves clinical outcomes [101].

While the existing evidence supporting the primary prevention in cardio-oncology is only suggestive and requires further validation [2, 43, 75, 102], the secondary prevention has already entered clinical practice guidelines despite persistent unresolved questions [103].

For the secondary prevention strategy, an identification of preclinical signs of cardiovascular toxicity is fundamental, in order to timely start an adequate treatment management and introduce cardioprotective and vasculoprotective strategies to prevent the development of asymptomatic or symptomatic vascular or cardiac dysfunction. Since cancer therapies can cause vascular and cardiac damage through various mechanisms in order to promptly establish a correct treatment, a careful assessment of vascular and cardiac function in cancer patients is crucial. Regrettably there is an urgent need for prospectively validated criteria of early cardiotoxicity to optimally manage and support patients at risk of cardiovascular complications [13].

Traditional Outcome Measures to Early Detection and Prediction of Chemotherapy-Induced Vascular Damage

To date the most common clinical diagnostic tools for the screening, risk stratification, and detection of cardiovascular toxicity are biomarkers and cardiovascular imaging, including three-dimensional echocardiography, speckle-tracking echocardiography, cardiac magnetic resonance, noninvasive assessment of flow-mediated dilation (FMD = flow hyperemic mediated dilation), carotid ultrasound scan to assess the increased intima-media thickness, arterial stiffness (AS) in order to identification of vascular changes in subclinical stages [104], multiple-gated acquisition (MUGA) scan, and cardiac magnetic resonance (CMR).

Patients who develop asymptomatic LV dysfunction or HF during cancer therapy are likely to profit from ACE inhibitors or angiotensin II receptor blockers (ARBs) and beta-blocker treatment similar to the general HF population. More specifically, patients with anthracycline-induced cardiotoxicity have a better cardiac outcome when treated with ACE inhibitors and/or beta-blockers early after detection of cardiac dysfunction, and combination therapy may be more effective than either treatment alone [16, 105].

LVEF is the most frequently used parameter to diagnose cardiotoxicity in clinical practice, and echocardiography and MUGA scans are largely employed in clinical practice for this purpose [6, 8, 13, 106–110]. An LVEF decrease (>10%) to a value <50% identifies patients with cardiotoxicity in both imaging modalities [13, 109]. Compared with echocardiography, MUGA provides the advantage of a high reproducibility, but it is hampered by significant disadvantages, such as cumulative radiation exposure [13, 108]. Confirming LVEF decrease by repeated cardiac imaging (preferably by echocardiography) 2 to 3 weeks after the baseline initial decrease in LVEF is strongly recommended, as well as categorizing LVEF reduction as asymptomatic or symptomatic and repeating echocardiography measurements during follow-up [13]. Although left ventricular ejection fraction (LVEF) is widely utilized in monitoring the cardiac function in clinical practice, it has not demonstrated high sensitivity in detecting subclinical myocardial dysfunction [111]; in fact the decrease of LVEF occurs only in end-stage not allowing for early preventive strategies. New parameters and new imaging techniques have been developed in order to overcome the limitations related to isolate evaluation of LVEF. Among the new techniques, speckle-tracking echocardiography has shown the highest sensitivity in detecting early alterations in LV function associated with future development of cardiomyopathy [13, 109, 112–114]. In particular, a global longitudinal strain (GLS) >15% relative percentage reduction from baseline can identify patients who are at risk for cardiotoxicity [13, 109, 115, 116].

Among the other imaging modalities, a good incremental value is provided by CMR, for the possibility of the method to perform a tissue characterization, identifying fibrosis and edema as well as by gold standard technique for LVEF

estimation [13, 117, 118] and by real-time three-dimensional echocardiography that can obtain a full-volume scan of the left ventricle, providing a quantification of volumes independently of geometrical assumption, although their availability is still limited.

At present, therefore, the left ventricular ejection fraction assessment represents the main standard practice for cardiac monitoring during cancer therapy, but it detects myocardial damage only when a functional impairment has already occurred, not allowing for early preventive strategies.

In the cardio-oncological setting for early diagnosis and detection of high-risk patients other than the imaging techniques, in the last decade, a newer approach based on the measurement of cardio-specific biomarkers has been widely demonstrated. The challenge with the available published data is the timing of the laboratory assessment relating to chemotherapy, the definition of the upper limit of normal for a specific test, the use of different laboratory assays, and the strategy to begin in case of an abnormal result [119, 120].

Studies have in fact demonstrated that troponins and natriuretic peptides can be correlated with findings from cardiac imaging for the early detection of cardiotoxicity [121, 122]. Not only the increase but also the pattern of the elevation, particularly a persistent increase after 1 month since treatment, added prognostic information. Conversely, persistently negative TnI identified low-risk patients who did not need a strict cardiac follow-up [123]. Patients with troponin increase may benefit from early cardioprotective treatment with ACE-Is [30]. In patients treated with trastuzumab, especially after previous exposure to anthracyclines, troponin I elevation can identify those who will develop LV dysfunction and who will not recover in spite of treatments for HF [124]. Few data indicated an increase of troponin in subjects administered sunitinib and sorafenib for metastatic renal cell carcinoma, who developed ventricular function impairment [125]. Measurements of TnI and BNP demonstrated a predictive capacity to mark the cardiotoxicity in case of high, cumulative anthracycline doses, whereas they are not as valuable for the detection of cardiac abnormalities in early stages or for revealing cardiotoxicity induced by nonclassical therapeutic agents [121]. In the last years, studies have shown that high-sensitivity C-reactive protein correlates with subsequent cardiac damage [126]. The usefulness of cardiotoxicity monitoring using markers of inflammation and oxidative stress was demonstrated in a cardioprotective setting as well as in vasculoprotective setting,using an ATII receptor blocker, during epirubicin treatment, a reduction of IL-6 and ROS occurred in correlation with an improvement in the parameters of myocardial function [127, 128]. Other potential cardiotoxicity markers under investigation in oncology are high-sensitivity C-reactive protein, heart-type fatty acid-binding protein (H-FABP), glycogen phosphorylase BB (GPBB), and circulating micro-RNAs galectin-3, soluble ST-2, myeloperoxidase, and fibrocytes [121, 129–132].

In spite of what was stated earlier, namely, that an abnormal biomarker result is indicative of an increased risk of cardiovascular toxicity, there is currently no clear evidence to withdraw or interrupt the anticancer therapy on the basis of a new abnormal cardiac biomarker result, and conclusive data are needed to establish whether biomarkers reliably predict clinically relevant late consequences of cancer treatment.

Regarding the vascular damage as previously reported, structural endothelial damage, endothelial dysfunction, acceleration of atherosclerosis, prothrombotic actions, and vascular inflammation are some of the underlying mechanisms of cancer therapy-related changes in vessel function. To date, a common standard approach that is useful in clinical practice for early detection of vascular complications such as atherosclerosis is missing. For an early detection of vascular complications, the first step is simply monitoring CV risk factors [13], assessing patient functional status, measuring blood pressure before cancer treatment, and optimizing antihypertensive therapy during treatment with a goal of <140/90 mmHg (particularly in patients treated with VEGF inhibitors). Moreover, the identification of patients with preexisting CAD in those

undergoing 5-FU is of paramount importance since this drug substantially increases the risk of developing myocardial ischemia with a vasospasm-recognized mechanism. In addition, it should be considered that clinical factors (cancer-, treatment-, and patient-related) could be related to an enhanced risk of venous TE in subjects administered tyrosine kinase inhibitors.

Increased levels of markers of endothelial dysfunction, such as endogenous inhibitors of nitric oxide and dimethylarginines, have been detected many years after antineoplastic treatment in long-term cancer survivors [120]. Therefore, monitoring of these markers or of brachial artery flow-mediated dilation, an established technique to identify endothelial injury, might help in the prediction of cardiovascular events after cancer therapy [133]. Other vascular parameters, such as carotid intima-media thickness, might also be used to characterize potential endothelial damage [134]. More recently, great emphasis has been placed on the role of arterial stiffness (AS) that could be used for early detection of vascular damage induced by conventional and new antineoplastic drugs, accurately to stratify CV risk in cancer patients and to improve therapeutic strategies during anticancer treatment [104, 135–138]. One of the earliest demonstrations of subclinical atherosclerosis with associated impaired ventricular arterial coupling in cancer survivals was made by Drafts et al. who found, by magnetic resonance imaging of the aorta, an early and abrupt increase of pulse wave velocity, a marker of arterial stiffness, in patients treated with low to moderate doses of anthracycline-based chemotherapy; furthermore, this increase was accompanied by a subclinical reduction in LVEF and strain [139]. More recently, a marked stiffening of large elastic arteries was demonstrated by applanation tonometry also in patients undergoing VEGF inhibitors [140]. Accordingly, ACEIs should be preferred because of their anti-stiffening properties in the aorta in hypertensive patients treated with anthracyclines and VEGF inhibitors. However, further studies are needed to determine the true predictive value and usefulness as a screening tool of these markers to detect endothelial dysfunction.

Early Detection and Prediction of Chemotherapy-Induced Cardiovascular Damage by OMICS Approach

Recently, there is growing interest on the "omics" technologies. The "omics" refers to innovative technology platforms such as genetics, genomics, proteomics, and metabolomics; it may offer novel and promising tools to detect cardioprotective and vasculoprotective gene modulators and targeting receptors, allowing us a more robust and predictable approach in cardiovascular protection and the early detection of cardiovascular toxicity and individual responses to antineoplastic drugs. In fact, transcriptomics, proteomics (including phosphoproteomics and redoxproteomics), metabolomics, and more nascent immune-omics can provide an inventory of data relating to changes in cellular levels of mRNA, proteins, protein modifications, metabolites, and immune activation during acute exposure.

To date the omics data available are limited to cardiovascular toxicity induced by antineoplastic agents. In the light of the importance of oxidative stress in the cardiovascular toxic mechanisms of several antiblastic agents, including anthracyclines, tyrosine kinase inhibitors, and antimetabolites, the identification of early biomarkers with redox significance—known as biomarkers of oxidative/nitrosative cardiovascular toxicity—can be detected by the "-omics" approach [141–143], allowing us the development of innovative cardioprotective agents therapies that can alter the redox system at key points, without disturbing the physiological role of oxidative stress [143].

A decrease in nicotinamide adenine dinucleotide phosphate (NAD(P)H):quinone oxidoreductase 1 activity and an increase in ROS production by NAD(P)H oxidases have been considered early biomarkers of anthracycline-induced cardiovascular toxicity [121]. The bulk of these studies to date are conducted in animal models exposed to anthracyclines, particularly because human tissue specimens (cardiomyocytes) are difficult to obtain. The large interindividual variability in developing anthracycline cardiotoxicity suggests that there may be a genetic predisposition.

In line with this view, many studies identified gene polymorphisms associated with increased risk of anthracycline-induced cardiovascular toxicity [144]. The careful analysis of genetic variants, therefore, can allow identification of the individual variability of the response to antineoplastic drugs, which may be essential for personalized medicine and to decrease the adverse effects of chemotherapy [145, 146].

To date significant single nucleotide polymorphisms (SNPs) associated with a higher risk of developing anthracycline-induced cardiotoxicity have been identified [147–150].

Another interesting and new field of study is the application of metabolomics in the early detection of cardiovascular toxicity. The metabolomics enable detection of low-molecular-weight metabolites (acetate, succinate, pyruvate, etc.) by a combination of mass spectrometry and/or nuclear magnetic resonance spectroscopy [151–155].

Fewer data are available on the epigenetics of antineoplastic drug-induced cardiotoxicity [156–161]. Particularly investigations of miRNA in vitro and in vivo in mice models have shown promise and have triggered interest for patients with ACIC [157, 161, 162]. Taken together, the biomarkers identified by the "-omics" approach are considered new marker, in the early detection of anticancer cardiovascular toxicity and for more careful patient selection, risk stratification, and prognosis. However, we have only begun to scratch the tip of the proverbial, since, in fact, the data available to date remain insufficient and medical breakthroughs continue to identify novel biomarkers. On these promising clinical decision tools, further studies are needed to find more robust approach in the treatment of the cardiovascular toxicity.

Surveillance of Chemotherapy-Induced Cardiovascular Damage

There are currently no evidence-based guidelines for monitoring of cardiovascular toxicity during and after cancer therapies in adults; guidelines in pediatric oncology are a matter of debate. Several recommendations are available; however, none specify how often, by what means, or how long cardiac function should be monitored [2, 163]. According to the recent ESC position paper, the exact timing of cardiovascular toxicity surveillance and frequency of imaging and/or biomarker sampling needs to be personalized to the patient in the context of the specific antineoplastic, therapy, total cumulative dose, treatment protocol and duration, and baseline CV risk [13].

In general terms, all patients receiving cardiotoxic chemotherapy should undergo a cardiac assessment, including LV function, at baseline, during treatment and after treatment completion. The choice of modalities depends upon local expertise and availability, and several important core principles should be considered. It is important that the same imaging modality and/or biomarker assay should be used for continued screening throughout the treatment pathway.

The use of biomarkers—troponins and natriuretic peptides—is encouraged by the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines on cardiovascular toxicity induced by chemotherapy; is included in the *Mayo Clinic Proceedings* for risk assessment, monitoring, and management model for patients undergoing chemotherapy; and is included among the American Society of Clinical Oncology Clinical Practice Guideline recommendations for Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers. However at present, this approach is not used routinely [8, 14, 164].

In conclusion, to date the evidence is lacking regarding the optimal surveillance strategy to positively impact clinical outcomes. Below the cardiovascular management of the patients treated with the anticancer drugs most frequently used will be explained.

Cardiovascular Management of Patients Treated with Anthracyclines

Early detection of cardiotoxicity rather than the cardiotoxicity is important in patients treated with adjuvant anthracyclines; in these patients a

baseline cardiac function and further assessment at the end of the treatment should be assessed, particularly in the presence of a high risk for cardiotoxicity. For higher-dose anthracyclines containing regimens, and in subjects with a high baseline risk, earlier evaluation of heart function after a cumulative total doxorubicin (or equivalent) of 240 mg/m2 should be considered [13]. Measurement of at least one cardiac biomarker—high-sensitivity troponin or a natriuretic peptide—may be considered at baseline, and determination of high-sensitivity troponin I has been suggested with each cycle of anthracycline-containing chemotherapy [8, 120].

Cardiovascular Management of Patients Treated with Anti-HErbB22

Since patients receiving anti-ErbB2 therapeutics frequently also receive anthracyclines, a baseline evaluation is always recommended. Typically, cardiac assessment is performed every 3 months during and once after completion of anti-ErbB2 therapies. An improvement in the early detection of cardiac dysfunction with troponins and GLS measurements every 3 months during adjuvant trastuzumab treatment has been demonstrated. Troponin dosage with every cycle may be considered in patients with a high baseline risk [13]. Given the variability in timing of trastuzumab-induced LV dysfunction, measurement of troponin with every cycle may be considered in patients with high baseline risk [124, 165, 166].

Cardiovascular Management of Patients Treated with VEGF Inhibitors

There is high variability in the time of cardiovascular side effects in the patients treated with VEGF inhibitors occurrence (early after treatment and delayed for several months). There are no standardized guidelines regarding the monitoring of these vascular complications, and the treatments are frequently based on expert consensus rather than trial data. Typically, cardiac assessment is performed every 6 months initially until stability in values of LVEF is achieved. With a high baseline risk, it is better to perform early clinical assessment in the first 2 to 4 weeks after starting targeted therapies. Hypertension or destabilizing previously controlled hypertension is a relatively common side effect of several anti-angiogenic drugs like bevacizumab, sunitinib, and sorafenib [13, 167, 168].

It is very important, therefore, to control BP before starting any treatment and accurately monitor its variations during the course of therapy. ACE inhibitors, ARBs, β-blockers, and non-dihydropyridine calcium channel blockers (amlodipine, felodipine) are proposed as first-line therapies [6, 167, 169].

Because decreased nitric oxide signaling plays a key role in the pathogenesis of hypertension [170], drugs that increase nitric oxide signaling, such as the nebivolol, may be considered as well as other beta-blockers with vasodilatory effects, such as carvedilol. Diltiazem and verapamil due to inhibition of cytochrome P450 3A4, and because many VEGF inhibitors are a substrate of this isoenzyme, should be avoided. To ensure efficacy and tolerance of antihypertensive drugs, follow-up is mandatory. Patients with resistant hypertension should be referred to cardio-oncology or hypertension specialist assessment to minimize interruption of VEGF inhibitors.

To prevent and treat vascular complications, such as PAD, antiplatelet therapy is recommended [13]. Significant stenosis (e.g., those of carotid arteries) may need stenting or surgery. Targeted therapy for PAH can be used temporarily or permanently.

Cardiovascular Management of Patients Treated with Fluoropyrimidines and Cisplatin

The myocardial ischemia is often a side effect of several cancer therapie, particularly fluoropyrimidines and cispaltin could cause, in the long term, vasospastic effect, endothelial injury and acute arterial thrombosis in the long term [171, 172].

The identification of patients with preexisting coronary artery disease and other cardiovascular disease is very important before initiating cancer treatment. Patients treated with pyrimidine analogues and cisplatin should be closely monitored for myocardial ischemia using regular electrocardiogram, and chemotherapy should be withheld if myocardial ischemia occurs [13].

Personalized Treatment of Chemotherapy-Induced Cardiovascular Damage by Omics Approach

The era of personalized medicine is well upon us; in this scenario, a critical step toward defining a correct personalized anticancer therapy is the identification of the genes and pathways altered in the tumor of the patient and the elucidation of their particular oncogenic role. Ushered in by the remarkable omics approach, personalized medicine promises a more precise determination predisposition, diagnosis, and prognosis of cardiovascular toxicity, earlier preventive and therapeutic interventions, a more efficient drug development process, and more responsive approach to preventive measurements. As stated above, in fact, the identification of genetic and epigenetic contributions to the variability of the response to drugs may be essential for realizing personalized medicine. The multiomics technology can be leveraged to better develop a cardioprotective approach identifying cardioprotective gene modulators and potentially useful therapeutic targets of the antineoplastic drugs-induced cardiovascular toxicity. This approach could change the current definition of cardiovascular toxicity, shifting from a clinical to a subclinical definition, based on earlier, more sensitive, and specific biomarkers [143] (Fig. 19.1) (Table 19.1)

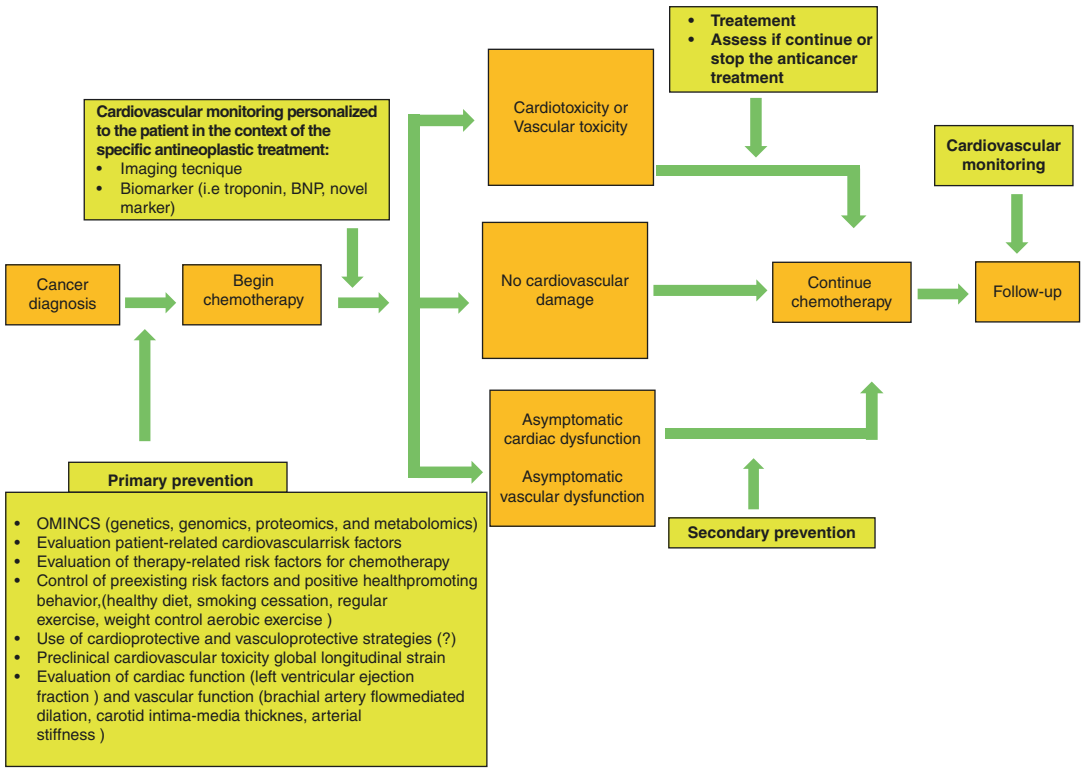

Fig. 19.1 Management of chemotherapy-induced cardiovascular toxicity

Table 19.1 Chemotherapy agents, principal cardiovascular complications, potential mechanisms, and prevention strategy

Chemotherapy drug class	Chemotherapy agents		Principle cardiovascular complication	Potential mechanism	Prevention strategy	Rationale
VEGF signaling pathway inhibitors	Antibodies Tyrosine kinase inhibitors	Bevacizumab Sunitinib Sorafenib Pazopanib Axitinib Neratinib Afatinib	Hypertension Ischemia Thromboembolism	Endothelial dysfunction ↓ NO signaling ↑Endothelin signaling Capillary rarefaction Vascular remodeling Oxidative stress Platelet activation ↓ NO and PGI2 signaling	ACE-1 and ARBs, β-blockers, dihydropyridine Calcium channel blockers, diuretics	Counteracting hypertension-dependent cardiac damage Lowering oxidative stress
Alkylating agents	Cisplatin		Hypertension Ischemia Thromboembolism	Endothelial dysfunction Platelet activation ↓ NO and PGI2 signaling Vasospasm		
Antimetabolites	5-fluorouracil		Ischemia	Vasospasm		
Anti-ErbB2	Trastuzumab				ACE-1, ARBs βblockers,	
Anthracyclines	Doxorubicin Epirubicin Idarubicin		Cardiotoxicity Negative arterial remodeling	Free radical damage Induced myocyte apoptosis DNA damage	β blocker ACE-1, ARBs HMG-CoA reductase inhibitors Physical exercise Dexrazoxane Lowering of lifetime cumulative doses Usage of epirubicin, less cardiotoxic than doxorubicin Avoiding bolus, preferring infusional Schedules	Preserving EGF signaling via a β-arrestin dependent mechanism, Lowering oxidative stress, improving lusitropy Lowering oxidative stress, reducing interstitial fibrosis, enhancing intracellular Calcium handling, cardiomyocyte metabolism, and mitochondrial function Dose-dependent cardiotoxicity

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Cardiovascular Damage in Clinical Trials

20

Enrico Bronte, Giuseppina Novo, Viviana Bazan, Christian Rolfo, Stefania Gori, and Antonio Russo

Introduction

During the last years, the improvement of survival and therefore the prognosis of cancer patients determined an outburst in the plan development for new molecules by pharmaceutical companies. Many drugs have been developed in recent years in oncology and hematology: molecular target therapies, including tyrosine kinase inhibitors, monoclonal antibodies, and immunotherapies. The purpose of the Food and Drug Administration (FDA) is to support public health by taking the necessary actions to protect it and regulating not only the development phase but also the post-marketing phase of the drug. Besides, the FDA safeguards that the drug needing approval is not only effective but also safe. Each drug determines its own set of adverse events often dose-related. Among these, of specific importance is cardiovascular toxicity which can emerge both during the experimentation of the molecule and during the post-marketing phase of the drug. Sometimes, a drug approved for clinical use can show a different cardiovascular toxicity profile, revealing toxicity percentages slightly higher than those highlighted during the study. This is linked to the fact that real-life data are different, because patients have often one or more comorbidity. So, they take one or various pills in addition to antineoplastic therapy. The instruments by which the post-marketing safety pharmacological data are reported are MedWatch, a FDA-sponsored adverse event alerting and recording program, data published in literature by several working groups around the world, and data entered in Expanded Access Programs, which include extensive clinical records often including thousands of patients [1–3].

Therefore, it is inevitable that the use of new drugs implicates different cardiovascular toxicity which should be described precisely to prevent them. Unfortunately, today there is not a stan-

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dardized method to assess cardiovascular risk, which defines how and when to stratify it during clinical trials [1].

Cardiovascular Screening in Oncologic Patients

The first findings of cardiotoxicity, which emerged from studies, were those related to anthracyclines. In fact, between 1980s and 1990s, the incidence of congestive heart failure (CHF) increased as the doxorubicin dose per square meter administered increased. The cardiac damage related to anthracyclines is related to the production of oxygen free radicals, which causes oxidative stress and determines alterations of the cardiomyocytes. These structural changes have been demonstrated at biopsy. So, this last evidence led researchers to conclude that an assessment of left ventricular systolic function was necessary at baseline and during treatment. This paved the way for a new approach to cardiovascular monitoring in oncology [4–6].

Moreover, basic research has shown that a perfectly functioning vascular network is crucial for the development, growth, and survival of solid tumors. In fact, if the necessary nutrients are not supplied by a proper blood flow to tumor cells, they are not able to grow and go to dormancy. Tumor vasculature is different from the one of a normal tissue. It is chaotic, disorganized, and lacking of a precise shape. Blood vessels of tumor vasculature have an altered endothelial cell physiology. For these reasons it is an alluring target for anticancer therapies. These drugs can be divided in two groups: vascular disrupting agents (VDAs) and vascular targeting agents (VTAs). VDAs cause vessels failure, so blood carrying nutrients and oxygen cannot reach the tumor. VTAs prevent the formation of new blood vessels and do not disrupt the already existing ones [7].

Chemotherapy was the first approach to cancer treatment. In the 1980s, the use of combination chemotherapy containing drugs such as etoposide, cisplatin, and bleomycin has brought to light Raynaud's phenomenon. Since that time various data were collected about acute and long-term vascular toxicity due to cisplatin-based chemotherapy. Hypertension was developed during and after a cisplatin-based chemotherapy in 15% to 54% of patients affected by germ cell tumors. Patients treated with chemotherapy had a three-fold more frequent hypertension than those not receiving chemotherapy. There was also an increase in cholesterol levels after treatment. It was evident that cancer survivors have an increased risk of dying for a disease linked to the circulatory system [8].

Radiation therapy is another important weapon in cancer treatment; in fact about 50% of cancer patients undergo a radiation therapy. Its mechanism of action is based on DNA damage of cancer cells. This event determines cell apoptosis and/or necrosis. Oxygen is a radiosensitizer. It interacts with radicals produced by radiation, so this event provokes DNA damage. This is confirmed by the fact that hypoxia has an important role in radiation resistance. Cells irradiated in air are much more sensitive to radiation therapy than those irradiated under a condition of severe hypoxia. The damage is sustained by radiation-induced endothelial cells apoptosis in tissue microvasculature. Normal endothelium is in a stable state; it has a low expression of VEGFR2. Irradiated tumor cells produce some cytokines that inhibit endothelial cells apoptosis. Among them there is hypoxia-inducible factor (HIF)-1. This last one is a transcriptional factor. It acts by regulating several processes, such as ATP metabolism, proliferation, and p53 activation. Under hypoxic conditions HIF-1 dimerizes. The resulting complex goes into the nucleus binding to VEGF promoter, so it determines an increased VEGF transcription. The agents targeting the angiogenic process can be divided in two types, which are monoclonal antibodies and tyrosine kinase inhibitors. These molecules influence the formation of new blood vessels. Some example of vascular damaging (or disrupting) agents are the cytokine tumor necrosis factor and the microtubule-destabilizing agents. Mixed inhibitors, such as EGFR inhibitors or neutralizing agents and cytotoxic anticancer agents, damage both tumor endothelial cells and malignant cells [9].

So, besides cardiovascular disorders highlighted using drugs targeting HER-2, new drugs have been developed over the last years such as monoclonal antibodies targeting VEGF, tyrosine kinase inhibitors targeting VEGFR, and mole-

cules inhibiting BRAF that have led to a wide spectrum of cardiovascular adverse events such as arterial hypertension, myocardial ischemia/infarction, thromboembolic events, and QT prolongation [10–16].

Another therapeutic option recently developed for cancer treatment is represented by immunotherapeutic drugs, also called immune system checkpoint inhibitors. These molecules were initially used for the treatment of metastatic melanoma, but lately their use has been expanded to many other types of cancer. These agents interact with specific molecules expressed on the surface of cells of the immune system, such as PD-1, PD-L1, and CTLA-4. So, the possible cardiovascular adverse events linked to these therapies have an autoimmune basis. It is the case of myocarditis, for example [17].

The assessment of toxicity during clinical trials is based on the document Common Terminology Criteria for Adverse Events (CTCAE): this establishes the criteria to define an adverse event and its degree. However, it has to be considered that the estimation can be variable, in particular, as regards the degree, from one observer to another, and thus some event could be underestimated [1].

Moreover, it has to be underlined that the classification of some pathological conditions has changed during the time. For example, it is clear that patients can have heart failure also if their ejection fraction is nearly normal, because of abnormalities of the diastolic phase and subtle abnormalities in the contraction of longitudinal fibers, not detectable by measuring ejection fraction. Accordingly, recently heart failure has been classified into (a) heart failure with preserved ejection fraction (HFpEF), in which ejection fraction is ≥50%, (b) heart failure with reduced ejection fraction (HFrEF) characterized by ejection fraction values ≤40%, and (c) heart failure with mildly reduced EF (HFmrEF) in which ejection fraction ranges between 41 and 49. The two conditions HFpEF and HFrEF have a 50–50 distribution. This aspect is noteworthy, since often ejection fraction values are considered as inclusion/exclusion criterion in clinical studies, while a patient can suffer of heart failure also if ejection fraction is not significantly reduced [18–20].

Current Approach to Cardiovascular Screening and Follow-Up in Patients Enrolled in Cancer Clinical Trials

The means for estimating adverse events for a certain clinical trial drug, including cardiovascular events, are established relating to pharmacodynamics and pharmacokinetics, hence in connection with the peculiar characteristics of the molecule. According to the current guidelines, basal cardiological evaluation in clinical trial includes determination of risk factors, measurement of blood pressure values and vital parameters, acquisition of the electrocardiogram, and ejection fraction (EF) measurement. These evaluations are then repeated at defined intervals to monitor cardiac performance over time.

Ejection fraction can be measured through radionuclide angiography (MUGA scan), echocardiography (echo), and magnetic resonance (CMR). As regards left ventricular dysfunction, it is defined as the reduction of LVEF of more than 10 percentage points or in any case until a value lower to the reference normal limit (50%, 53%, or 55% according to different recommendations) or the presence of symptoms of heart failure (HF) in association with a reduction of LVEF [3, 21, 22].

Echocardiography is the most used method, today, among the three mentioned procedures, for its wide availability and low cost. But it has some limitations, particularly the operator dependence. In fact, there could be an inter-operator difference in the ejection fraction value estimation of about 6% with the 3D technique and 13% with the 2D technique. This highlights how the 3D technique is more accurate than the 2D technique.

CMR is usually reserved to those patients whose echocardiographic evaluation is suboptimal because of poor image quality and controversial measurement of LVEF or in those in which it is necessary to suspend the antineoplastic treatment due to CTRCD. CMR could also be useful for the identification of subclinical damage. CMR is particularly useful in case of extra-cardiac masses that determine a functional impairment for extrinsic compression. Furthermore, CMR

permits to identify edema and fibrosis, and therefore it represents the best not invasive technique in the evaluation and diagnosis of myocarditis. Unfortunately, even this method has limits because it is not widely available, quite expensive, and cannot be performed on claustrophobic patients [1, 3, 21, 23–25].

MUGA scan has been used since the 1970s as one of the first-line imaging modalities for baseline and serial assessment of LVEF for cardiotoxicity. A problem in the use of this technique is the exposure to ionizing radiation of the patient. Furthermore, it does not permit evaluation of right ventricular function and atria and to study valves and pericardium. Compared to CMR, MUGA is less accurate in the estimation of LVEF. A study compared the accuracy of LVEFs obtained by contemporary clinical MUGA in cancer patients with reference LVEFs from cardiovascular magnetic resonance (CMR). Authors highlighted that MUGA LVEF values are only modestly accurate when compared with the values obtained from CMR. Using the thresholds of 50% and 55% of LVEF, there was a misclassification of 35% and 20% of cancer patients, respectively, to either normal or abnormal categories [26].

Hypertension is another important issue, particularly in patients treated with anti-angiogenic drugs, such as bevacizumab, ramucirumab, aflibercept, and tyrosine kinase inhibitors targeting VEGFR, such as sunitinib, sorafenib, and pazopanib. The etiopathogenetic mechanism is based on endothelial dysfunction. This event is associated with the reduction of nitric oxide bioavailability, the increased production of renal and vascular endothelin, the increased vascular tone, the decrease in microvascular density, and the renal thrombotic microangiopathy. Hypertension may occur alone, or it could be associated with other adverse events and, in particular, with ejection fraction reduction. For this reason, it is necessary to measure blood pressure at baseline and revalue it at each visit [27–29].

In clinical trial blood pressure measurement is performed by a nurse or a physician. They carry out at least two measurements with an interval of 1 minute at each visit, with a repeated measurement if there is uncertainty or distraction. Besides, if there is >5 mm Hg difference between the first and second measurement, additional (one or two) readings should be obtained and then the average of these readings is used. Patients should be encouraged to relax and keep silent for a few minutes before measurements. The evaluations have to be performed with the individual sitting with back support and legs uncrossed, keeping the upper arm at the midpoint of the sternum, through a support. In some patients, it is necessary that blood pressure is measured with the patient standing or lying. Furthermore blood pressure should be measured in both arms. If there is a significant difference between the two arms, the blood pressure value measured in the arm with the higher pressure should be used. Clothes that cover the arm should be removed. These evaluations are repeated at each visit, before treatment, during treatment, and after treatment suspension [30].

During the development of a new molecule, among the several possible cardiovascular adverse events, the delay of cardiac repolarization does not have a marginal role. The mechanism by which drugs can interfere with cardiac repolarization is the block of the repolarizing current of potassium, known as IK_r, and a delay in the inactivation of the sodium channels. It results in an elongation of the duration of the action potential, and consequently to the duration of the QT interval, which puts the patient at risk for a potentially fatal form of ventricular tachycardia, known as torsades de pointes (TdP). Its most severe form rapidly degenerates into ventricular fibrillation and therefore into sudden death. TdP usually starts with a prolonged QT interval over 500 milliseconds. It is frequently preceded by a sequence, called *short-long-short*. This sequence includes a pause that extends further the QT interval and facilitates the achievement of a threshold through an electrical activation, which is known as "early after depolarization" (EAD). This can initiate ventricular tachycardia through the mechanism called "triggered activity" [31–34].

The elongated QTc syndrome is commonly associated with specific genetic mutations. In oncological patients, it is mostly related to the drugs interferences or to electrolyte disturbances related to vomiting or diarrhea.

To identify eventual QT prolongation induced by the studied drug, clinical trial contemplates the registration of ECG with calculation of QT corrected for the heart rate (QTc). This can be obtained using the Bazett's formula. If a relationship between the study drug and the prolongation of QT interval is detected, it is necessary to establish what is the cut-off beyond which this molecule determines a pharmacological effect. QTc >500 ms or QTc prolongation >60 ms from the baseline value should be considered an alert value and worth drug discontinuation [31, 35].

Over the years, researchers increasingly studied various biomarkers, for early assessment of cardiotoxicity, but it has been not established a precise timing for measuring them in clinical practice. Biomarkers are currently not studied in oncological clinical trials. For clinical trials, concerning fields not related to the topic of cardiovascular diseases, there are not guidelines for cardiovascular disease management. Moreover in these kinds of studies, the evaluation of cardiovascular adverse events and endpoints is carried out by physicians other than cardiologists. Thus, to avoid incorrect estimation of cardiotoxicity, a new document has been produced from the collaboration between FDA and the Cardiac Safety Research Consortium (CSRC). In this paper, the authors defined some key points to make cardiovascular adverse events evaluation homogeneous for clinical trials developing new drugs. Among these, there are: (1) to prefer a prospective evaluation of an adverse event rather than a retrospective one; (2) each researcher should review the cardiovascular adverse event independently, without conditioning by other researchers—besides he/she should have the possibility of referring to a reviser who has extensive experience in the study field of the adverse event—(3) to carry out the evaluation of an adverse event with the support of a case report form (CRF), which can guide the researcher through specific questions in the detailed description of the event; (4) to define cardiovascular events that were not previously highlighted during clinical trial, especially if there is a strong biological rationale that justifies it or if characteristics suggest heterogeneity; and (5) to consider interregional variability, especially in international studies [36].

How to Optimize Cardiovascular Damage Management of Cancer Patients Enrolled in Clinical Trials

In the field of oncology, clinical trials usually evaluate blood pressure according to CTCAE criteria. These criteria only estimate the degree of severity of the event. Instead the Joint National Committee (JNC) criteria, used in cardiology, include hypertension management parameters. CTCAE criteria are unsatisfactory in clinical trials studying new molecules not only for hypertension identification but also in defining an adverse event. Besides, hypertension is not related to time duration or also to the evolution in time. In some studies, researchers defined and classified hypertension accurately; in this way, hypertension had a predictive effect of therapeutic response. For this reason, it is advisable, when a clinical trial starts, to establish a more comprehensive assessment of hypertension, including management parameters. Recently, data about apatinib were published. It is a new VEGF inhibitor studied in advanced breast cancer. It has shown that the presence of hypertension affects the outcome of the patient. Studies did not use common criteria for the evaluation of hypertension [37–40].

As regards the ventricular function, today, some clinical studies in the field of oncology do not include LVEF measurement. This is due to the fact that, during the preclinical and the initial clinical phases, this type of toxicity has not been highlighted or the pharmacodynamic characteristics of the molecule did not raise the suspicion of cardiac toxicity. However, it would be better to always perform echocardiographic monitoring in consideration of what has been enunciated so far. Moreover, if there is not a reduction of LVEF value, this does not imply that there is not any cardiac damage.

In fact it is well known that ejection fraction is not a sensitive marker for identifying subtle variation of myocardial contractility and that it changes when damage related to antineoplastic drugs is already occurred. It is possible to evaluate subclinical cardiac damage with the support of echocardiographic myocardial deformation indexes, such

as strain, strain rate, and twist, whose reduction has been shown to precede the reduction of LVEF values. Some studies have recorded a reduction in global longitudinal strain (GLS), which is usually measured through speckle-tracking echocardiography (STE), in patients undergoing treatments with anthracyclines or trastuzumab. GLS is today considered the best imaging parameter for the early detection of subclinical damage. A reduction in the value of GLS of more than 15% from baseline value is considered clinically significant, while a reduction of less than 8% is not clinically significant [21, 24, 25, 41]. Therefore, in clinical trials, baseline evaluation should advisably include measurement of myocardial strain.

For a better assessment of QTc, it is important to record and describe any adverse event that could be responsible for its prolongation. Researchers should carry out a careful medical history, evaluating and recording those conditions that increase the risk of arrhythmia, such as old age; female sex; pro-arrhythmic drug assumption; electrolyte alterations, including hypokalemia, hypocalcemia, and hypomagnesemia; or the presence of comorbidity, such as congestive heart failure, bradycardia, or hypertrophy of the left ventricle. Besides, it is very important to evaluate all the possible risk factors that contributed to that event, such as, for example, a genetic susceptibility (long QT syndrome). As emerged from some studies, the evaluation of the QTc must consider the "ER analysis" that is the exposure-response analysis. It evaluates the real effect that the drug has on the QTc. Another important aspect is the post-marketing phase considering that adverse events such as TdP, cardiac arrest, sudden cardiac death, or ventricular arrhythmias can become evident only on larger patient populations [3, 35, 42].

Patients at increased risk of arrhythmias should perform an electrocardiogram monitoring, during anticancer drug infusion. Besides, some adverse events can occur late since drug administration; for this reason, in particular cases, it could be useful the implantation of a loop recorder, for home monitoring. This device is able, through the support of a communicator to monitor the rhythm even during sleep and to report any alert to the monitoring cardiac center [43, 44].

For the study and identification of vascular damage, there are various methods that could be used in cancer patients enrolled in clinical trials. Ultrasound scan of carotid arteries with intima-media thickness (IMT) measurement, vascular reactivity, and baroreflex sensitivity are some of them.

A study evaluated carotid intima-media thickness measurement as instrument to ameliorate cardiovascular risk stratification in head and neck cancer patients. Besides the authors compared it to the standard cardiovascular risk calculators recommended in the Adult Treatment Panel III guidelines and in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the assessment of cardiovascular risk. They highlighted that both Framingham risk score (FRS) and pooled cohort atherosclerotic cardiovascular disease (ASCVD) risk calculators underestimated the level of risk of cardiovascular events compared to carotid intima-media thickness measurement. They showed that about 74% of head and neck cancer patients who underwent radiotherapy were at high risk for cardiovascular events using the intima-media thickness technique. Besides, half of these patients had a change in clinical management. On the other hand, FRS and pooled cohort ASCVD risk equation did not recognize about 40% of the cases that were treated as at high risk of developing cardiovascular events. This demonstrates that risk calculators, although are useful tools, do not perfectly correlate with subclinical atherosclerosis and true cardiac risk, while carotid intima-media thickness is more precise [45].

A role in clinical studies could also have the evaluation of the coronary artery calcium (CAC) score. This one quantifies the calcification levels of coronary arteries. The CAC score could be used to better stratify the risk in patients considered to be at intermediate risk by the conventional score. It could give indications for a better diagnostic and therapeutic management of the patient [3, 46].

The evaluation of endothelial function also assumes a specific importance because it is the first step of atherogenesis, even though it has to be noticed that nowadays it is little used in clinical trials in oncology. Instrumental technique, that would be useful to study it, is the evaluation

of the flow-mediated dilation of the brachial artery. The hypothesis is that it reflects the flow-mediated dilation of the coronary arteries, thereby predicting long-term cardiovascular events. These methods assume value and relevance considering that they are not invasive, low cost, and repeatable [3, 47, 48].

The use of concomitant medications can alter the action of VDAs inhibiting or potentiating their effects. This effect would be evident in clinical but not in preclinical investigations. The pharmacokinetics of drugs is pivotal. Besides, molecular biomarker data could explain why some subpopulations of patients are more prone to toxicity. For this reason, it has become increasingly evident that such evaluations are necessary for a proper identification of these subsets of patients [7].

To study the vasculature, there are various radiologic methods, but they mostly have the limitation to show a static snapshot of microvascular function. Studying the functional dynamics of microvasculature would be much more useful. The possibility to temporally monitor how blood vessels respond to metabolic changes and physical demands is very fascinating. Today, there are two types of procedures to study this aspect: focal and whole organ assessment. The focal procedures regard the study of the skin and include laser Doppler flowmetry of blood flow, transcutaneous oxygen tension, and iontophoresis. The whole organ study procedures include electron-beam computed tomography (CT), magnetic resonance imaging (MRI), and intravascular Doppler ultrasound. They are used to evaluate blood volume changes in response to vasoactive agents such as acetylcholine. Unfortunately, each procedure has its limitations; besides it has not been yet validated a not-invasive 3D technique for the assessment of microvascular functional dynamics. A novel 3D MRI-based technique is in development for this type of assessment to study near real-time blood volume changes in whole organs in vivo.

The authors developed an optimized gas challenge protocol that permits an accurate assessment of microvascular tone control. This is carried out through the induction firstly of vasoconstriction, using air with altered levels of carbon dioxide (CO_2) and oxygen (O_2). The inhalation of elevated CO_2 levels (moderate hypercapnia) and lowered O_2 levels (hypoxia) stimulates changes in blood volume in normal physiology, so the measurement of such changes can assess vascular tone modulatory capacity in response to stress. This is an active process. In a later time, there is the second phase of vasodilation, which is a relaxation process [49].

Much still needs to be done to find biomarkers that could support researchers in the study of cancer patients included in clinical trials.

Inflammation and thrombotic pathways activation play an important role in the pathogenesis of atherosclerosis, atherothrombosis, proliferative vasculopathy, and vasospastic vasculopathy. The key players that determine the occurrence of a clinical event are endothelial cells, smooth muscle cells, platelets, monocytes, and proteins for the formation of clots. Inflammatory biomarkers include high sensitivity reactive protein C (hsCRP) and IL-6. These biomarkers have shown to be correlated to the generation of cardiovascular events. Other biomarkers that could have a role in predicting the risk of developing a cardiovascular event are soluble ICAM-1, soluble P-selectin, and MRP-14 [3, 50, 51].

The most studied biomarkers today in oncology field are troponin I (TnI) and natriuretic peptides. TnI is considered the gold standard in diagnosing myocardial damage. It has been shown in some studies that TnI increase exposes patients to a greater risk of developing a cardiovascular event. Besides, an increase in TnI levels is directly related to the severity of events due to the oncological therapy. Elevated levels of troponin were reported to predict the reduction of left ventricular ejection fraction. The brain natriuretic peptide (BNP) and its amine terminal portion (NT-proBNP) have been studied in patients treated with chemotherapy. The increase in the levels of these molecules is closely related with an increase in filling pressures. In addition, it has been shown in some studies that an increase in its levels is marker of increased risk to develop cardiac adverse events related to treatment. Biomarkers are reproducible and low cost, with a

high negative predictive power. They are not operator-dependent (differently from left ventricular ejection fraction measurement). However, there is no consensus among experts concerning their use because the results of the studies evaluating these biomarkers are often ambiguous, and the study populations are small and not homogenous. Particularly there are insufficient evidences to understand pathophysiological importance of mild increases in troponin, uncertainty about the timing of measurement and not uniform reference values according to the different dosing methods used [21, 22, 52, 53].

Recently circulating microRNAs (miRNAs) have become increasingly important in cardiovascular diseases. For example, miR-181 inhibits the atherosclerotic process and regulates the inflammatory process of endothelial cells, limiting the activation of NF-κB, the expression of inflammation genes, and leucocyte accumulation [3, 54]. Evaluation of microRNA could provide important prognostic information.

The integration in clinical trial protocols of the measurement of one or more biomarkers could permit a better management of toxicity in the subsequent phase in which the drug is approved and entered into the market for clinical use. In geographic areas where hospitals have many patients but sometimes lack of the necessary equipment or dedicated staff, technology support could help. In fact, technological progress has led during the last years to the development of electronic equipment able to carry out remote diagnostic tests with robotic supports. A study also evaluated the feasibility of a cardiologic consultation using a remote robotic-assisted echocardiography on a small group of patients. It highlighted that if on the one hand the quality of the consultation was not compromised, on the other hand there was a good level of satisfaction by patients [55].

In Table 20.1 we propose a scheme to evaluate cardiovascular risk and monitor the occurrence of cardiovascular toxicity in patients enrolled in clinical trials.

Expert Opinion

Based on these premises, there are potential biases in the evaluation of cardiotoxicity during a clinical trial for the development of a new oncological drug (Fig. 20.1). The clinical cardiovascular toxicity of a drug is not always predictable from in vitro or animal studies, which can lead to a not adequate characterization of the clinical toxicity before the drug is approved for clinical use and goes to the market. It follows that researchers often do not adequately study the treatment strategies needed to avoid cardiovascular adverse events. The consequential effect of this would be that potential cardiovascular problems remain misdiagnosed during the study of a drug and in those of subsequent generations. The FDA defined, during the recent workshop dedicated to this topic, the not-clinical steps to be fol-

Table 20.1 Scheme of cardiovascular evaluation proposed during a clinical trial

	Screening visit	First month visit	Third month visit	Sixth month visit	Ninth month visit	First year visit
General visit and medical history	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓	✓
Vital signs (e.g., blood pressure)	✓	✓	✓	✓	✓	✓
ECG (QTc, PR, QRS)	✓	✓	✓	✓	✓	✓
Echo (LVEF, GLS)	✓		✓	✓	✓	✓
Echo of the supra-aortic trunks	✓			✓		✓
CMR	To be performed in specific cases					

Note: *Make additional measurements of one or more of these parameters, if necessary*

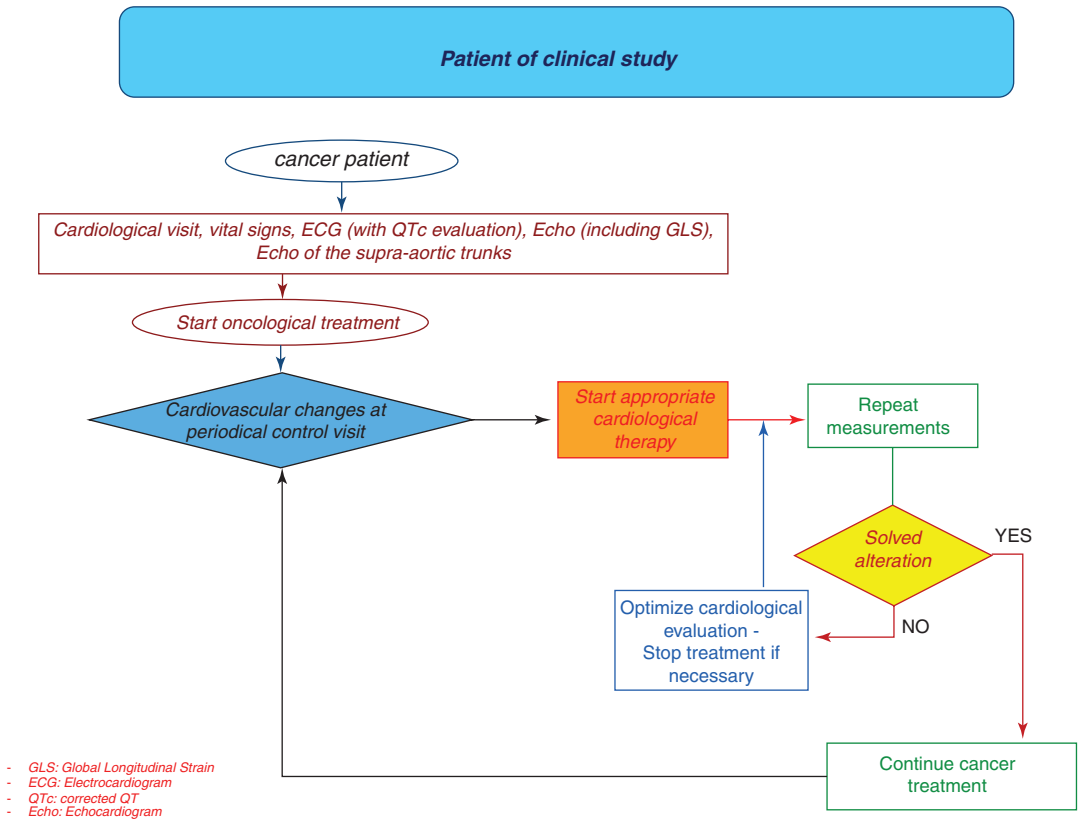

Fig. 20.1 Flow chart of the proposed cardiological evaluation in patients enrolled in a clinical trial

lowed in clinical trials for the development of new drugs in oncology in order to define the cardiovascular safety profile.

In vivo and in vitro not clinical studies ((ICH S9) International Conference of Harmonization) should firstly define (a) the level of a potential risk and comprehend the mechanism underlying it and (b) identify those cases in which cardiovascular safety studies are necessary and the related timing. These studies must be used (1) as preparatory studies for the development of drugs that are used for life-threatening oncological pathologies and (2) to give recommendations on the type and timing of not-clinical studies specific to the development of a certain anticancer drug, (3) as they are preparatory to studies that develop small molecules and synthesized drugs according to biotechnology processes and (4) they are a guarantee in facilitating and accelerating the development of anticancer drugs and protecting patients from predictable adverse events.

If this model highlights cardiovascular problems, which could give additional risks during clinical trials, appropriate pharmacological studies should be considered and carried out (ICH-S7A and/or S7B). The principles, on which not clinical studies are based, are essentially linked to the Safety Pharm endpoints In Toxicology Trials (SPiT). This is an acronym to indicate pharmacological safety endpoints in toxicology studies. This model consists of a mixture of pharmacological safety meaning an acute effect and toxicity meaning chronic exposure. This is also defined through in vivo and in vitro models with the support of composite parameters that tend to identify a limit level of cardiovascular safety and a more defined risk assessment. The advantage of this model is that it has multiple endpoints over long-term periods. The weaknesses are the risk of

false signals, unpredictable time interval for the appearance of an event, and not verified transfer to human being.

If on the one hand the only CTCAE criteria seem scarce to be up against the complexity of a possible cardiovascular problem and the variety of oncological clinical trials currently underway, on the other hand, the improvement of the models for cardiovascular safety assessment is not without problems. A study evaluated the adherence of oncology randomized clinical trials to the latest version of CTCAE (v3.0) through the evaluation of the quality of reporting of adverse events in publications. It shows the evidence of poor reporting of toxicity in clinical trials. It highlighted that the subjective adverse events, such as fatigue, might be variable when they were assessed by different health practitioners, while the objective adverse events are generally more consistent and accurate when they are supported by laboratory or imaging data.

A newly developed instrument in the optimization of the quality of the adverse event reported is PRO (patient-reported outcome)-CTCAE, which is designed to systematically capture symptomatic adverse events from patients and complement clinician-rated CTCAE.

An important dowel in the mosaic of cardio-oncology could be represented by genetic analysis and the study of polymorphisms, which could permit to explain toxicity and their mechanisms, because often these are not fully understood.

The formation process of a cardiovascular injury is a multistep process, as already known. Its steps could have different intervals depending on present risk factors and the possible appropriate corrective therapies implemented at each step [3, 18, 56–59].

Radiogenomics is the discipline that studies genetic differences as response to radiation therapy. It evaluates patient variability in relation to radiation. It investigates if there is a possible genetic background for different responses to radiation through the study of single-nucleotide polymorphisms (SNPs) in selected candidate genes and the screening of multiple genes using gene expression arrays. The rationale of this type of study is based on the fact that SNPs generate a not-conservative amino acid change in the final gene product or they are part of regulatory regions that possibly affect gene expression or protein secretion rate. Studies evaluated the combined effect of a couple of SNPs; it emerged that carrying more than one SNP was significantly associated with early side effects in normal-weight patients exposed to radiation. Even though, it must be considered that this is a data-generated hypothesis. So, it requires validation in an independent study. Furthermore, SNPs importance has been studied in patients affected by glioblastoma and treated with an anti-angiogenic drug, bevacizumab. A genome-wide analysis of genetic variation associated with the vascular toxicities was carried out in 367 patients. Hypertension was strongly associated with bevacizumab, and the risk assessment was increased by the presence of polymorphisms [60, 61].

By transferring this solid algorithm about the formation of an injury to an oncological treatment, it would be beneficial for a trial to insert among the inclusion criteria for cardiovascular problems the sum of a step process, a sort of index for the patient, that considers as first element the risk stratification through a sure definition of the existing risk factors, imaging (such as LVEF), and biomarkers. The second step would be the necessary specific therapeutic intervention based on the baseline risk. This last one is defined by the type and duration of the planned oncological treatment. The last step would be to define cardiovascular outcomes for a certain patient or surrogate outcomes that should be pursued and maintained during the oncological treatment.

Conclusions

Measuring and monitoring cardiovascular function in oncology is essential, because oncological patients treated in everyday practice have an average medium to high cardiovascular risk. This is also important since cardiovascular diseases represent the first cause of death in the world. The increase of survival in oncology, especially in certain types of cancer, exposes patients to a greater cardiological risk than the only oncological

one. So, diseases, such as heart failure, valves diseases, vascular diseases, or cardiomyopathy, could have a significant long-term prognostic impact.

The correct baseline evaluation and subsequent checks of patients included in clinical study protocols are not easy to define. The involvement of a cardiologist in the clinical study could certainly improve the identification of cardiovascular toxicity of anticancer drugs in clinical trials. This should be preferably performed in a dedicated ambulatory for oncological patients in profit clinical trials, that is, the cardio-oncology ambulatory for clinical trials.

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