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IM - REVIEW

Cardiovascular toxicity of anticancer-targeted therapy: emerging issues in the era of cardio-oncology

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Abstract Over the last decade, the advent of molecular targeted therapy radically changed the treatment of several forms of cancer. However, these innovative anticancer drugs, namely monoclonal antibodies and small molecule tyrosine kinase inhibitors were found to adversely affect cardiovascular function. These "on-target" and "off-target" drug side effects encompass a wide range of cardiotoxicities, including left ventricular dysfunction leading to heart failure, electrocardiographic abnormalities with dysrhythmias, hypertension, myocardial ischemia and thromboembolic events. The unclear incidence of drug-induced cardiovascular events together with uncertainty on their reversibility and long-term safety call for a multidisciplinary effort embracing cardio-oncological expertise supported by primary care physicians, pharmacologists and toxicologists. Here we address emerging cardiovascular events associated with targeted anticancer drugs by offering a concise review on: (1) mechanistic basis subtending cardiotoxicity and (2) clinical advice for effective patient management (i.e., detection, treatment, monitoring and reporting of cardiovascular side effects). In this scenario, onco-vigilance (i.e., pharmacovigilance oriented to oncologic drugs) is emerging as a key to support cardio-oncologists inappropriateness.

Keywords Cardiotoxicity · Targeted therapy · Pharmacovigilance · Monitoring

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Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AIFA	Agenzia Italiana del FArmaco (Italian Regulatory Agency)
ATE	Arterial thromboembolism
BP	Blood pressure
CHF	Congestive heart failure
CTCAE	Common terminology criteria for adverse events
ECHO	Echocardiography
EGFR	Epidermal growth factor receptor
GIST	Gastrointestinal stromal tumor
HER2	Epidermal growth factor receptor 2
LVEF	Left ventricular ejection fraction
mAbs	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
NO	Nitric oxide
PDGF	Platelet-derived growth factor
RCC	Renal cell carcinoma
SPC	Summary of product characteristics
TKI	Tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous thromboembolism

Introduction

Cardiotoxicity with anticancer therapy represents a substantial health burden, and is now perceived as one of the most significant complications of oncologic agents, not only for "old-fashioned" chemotherapeutics (i.e., anthracyclines), but also for the so called "targeted drugs" (i.e., compounds acting through inhibition of a specific target

molecule) [1]. Among these, monoclonal antibodies (mAbs) and small molecule tyrosine kinase inhibitors (TKIs) have been recently recognized to carry an unwanted (and unpredictable) effect on the cardiovascular system (Table 1) [2].

The National Cancer Institute defines cardiotoxicity in general terms as "toxicity that affects the heart" (http://www.cancer.gov/dictionary). This definition embraces a variety of side effects affecting both the heart and circulation: valvular injury, dysrhythmias, changes in blood pressure (BP), arterial/venous thrombosis or impairment in myocardial contraction or relaxation (i.e., systolic and diastolic dysfunction) (Fig. 1). From the clinical standpoint, drug-related cardiotoxicity has been defined by the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials as one or more of the following: (1) cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF), either global or more severe in the septum; (2) symptoms associated with congestive heart failure (CHF); (3) signs associated with CHF (e.g., tachycardia); (4) reduction in LVEF from baseline that is in the range of less than or equal to 5% to less than 55% with accompanying signs or symptoms of HF, or a reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without accompanying signs or symptoms [3]. Notably, the severity of these cardiovascular toxicities may range from asymptomatic subclinical abnormalities such as LVEF decline to life-threatening events such as acute ischemia.

Cardiovascular safety currently represents a challenging aspect for drug developers, regulators, basic researchers and clinicians, who are exploring strategies to predict and detect cardiotoxicity [4]. Several initiatives and consortia have been created to act synergistically to move beyond the current state of knowledge [5]. From the regulatory standpoint, QT prolongation with associated *Torsades de Pointes* is recognized as a key cardiovascular safety liability deserving appropriate investigation. This topic has already been extensively covered [6] and, therefore, will not be addressed in the present review.

Anticancer-induced cardiotoxicity represents a rapidly evolving field with clinical implications for primary care physicians who play a pivotal role in managing practical issues such as hypertension. The aim of this review is to address emerging cardiovascular events associated with targeted anticancer drugs, focusing on left ventricular dysfunction/heart failure, hypertension and thromboembolism, which are critical inter-related aspects in the oncological setting. We offer an overview on (1) mechanistic basis subtending cardiotoxicity and (2) clinical advice for effective patient management (i.e., detection, treatment, monitoring and reporting of cardiovascular side effects).

Unsolved clinical issues: the need for a translational cardio-oncological approach

Cardiovascular safety in patients with cancer represents an emerging clinical issue, especially for targeted drugs, which were optimistically designed to spare systemic adverse effects. The precise magnitude of the problem is actually undefined, but several epidemiological reasons may partially contribute to increase the burden of this phenomenon: (1) the increasing number of cardiotoxic anticancer drugs entering the pipeline; (2) the significant improvement in life expectancy of oncologic patients, thus requiring long-term monitoring and (3) similarities between cancer and cardiovascular diseases in terms of incidence (exponentially age-related), risk factors and pathogenesis [7]. All these aspects strengthen the importance of predicting drug-related cardiac dysfunction in drug development, preventing and identifying high-risk patients through accurate clinical monitoring.

Although efforts have been directed towards risk prevention, several issues are still unsolved, especially for targeted agents. First, the long-term risk of cardiotoxicity associated with targeted therapy appears to be largely underestimated, mainly because clinical trials do not necessarily reflect clinical practice (e.g., presence of co-morbidities and risk factors). Therefore, active surveillance is warranted to assess the impact of the problem. Second, little is known on the reversibility of the phenomenon, especially for TKIs. Third, the question arises whether or not we are dealing with a class effect (i.e., shared by all agents of a given pharmacological class).

The main clinical issue to be clarified regards the uncertainty surrounding definition and assessment of cardiac dysfunction [8]. Despite universal adoption, LVEF does not represent the flawless method to evaluate cardiac functional reserve: because of its inherent subjectivity in the interpretation of LVEF as assessed by echocardiography (ECHO), a drop in this parameter does not always reflect cardiac injury. Conversely, a stable LVEF should not be taken as evidence of lack of cardiotoxicity. Moreover, there are different approaches in monitoring LVEF among trials (e.g., a single LVEF drop vs. an absolute decline of at least 10 percentage points from baseline). Given the inconclusive evidence from clinical experience, a step back to basic science is advisable to gain insight into mechanisms underlying cardiotoxicity. First, during the early phases of drug development the predictability of preclinical screening models should be clarified: insights into relevant molecular mechanisms involved in the pathophysiology of CHF may pave the way to expand therapeutic options of physicians. Moreover, lessons and experience gained from approved TKIs encourage

Table 1 Summary of cardiovascular side effects associated with targeted drugs with recommendations to support appropriate management and monitoring other major toxicities in clinical practice

Drug class/ agent	Molecular target(s)*	Therapeutic indication(s)	Cardiovascular toxicities with relevant frequency#	Other toxicities of important clinical impact	Recommendations/advices
Drugs with a recognized risk					
TKI					
Imatinib	**ABL1/2**, **PDGFRα/β**, **c-KIT**, hERG	CML, Ph^+ B-ALL, CMML, CEL, GIST	Warnings for fluid retention Common: flush, hemorrhage Uncommon: palpitations, tachycardia, CHF, pulmonary oedema, hypertension, hematoma, hypotension, Raynaud Rare: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion Unknown: pericarditis, cardiac tamponade	Hematological toxicity (neutropenia, thrombocytopenia and anemia) Drug interactions (CYP3A4)	Electrocardiogram monitoring at regular intervals (before and during treatment) and attention to electrolyte imbalance (especially hypokalemia and hypomagnesemia) Dose adjustment according to the severity of hematological toxicity Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice) Due to the risk of pulmonary arterial hypertension with dasatinib: close monitoring for signs or symptoms of cardiac disease; consider echocardiographical evaluation in case of pre-existing risk factors and drug withdrawal/dose reduction Vigilance for potential severe peripheral artery disease associated with nilotinib
Dasatinib	**ABL1/2**, **PDGFRα/β**, **c-KIT**, NRTK (Src family), hERG	Resistant CML and Ph^+ B-ALL	Warnings for QT prolongation, fluid retention and pulmonary arterial hypertension Highly common: hemorrhage (excluding gastrointestinal and CNS) Common: CHF/cardiac dysfunction, pericardial effusion, arrhythmia (including tachycardia), palpitations Uncommon: myocardial infarction, pericarditis, ventricular arrhythmia (including tachycardia), angina pectoris, cardiomegaly Rare: cor pulmonale, myocarditis, acute coronary syndrome		
Nilotinib	**ABL1/2**, **PDGFRα/β**, **c-KIT**, hERG	Resistant CML	Warnings for QT prolongation and sudden death Common: hypertension, flush, angina pectoris, arrhythmia (including A-V block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, QT prolongation Uncommon: hypertensive crisis, hematoma, CHF, pericardial effusion, coronary disease, cyanosis Unknown: hemorrhagic shock, hypotension, thrombosis, myocardial infarction, ventricular dysfunction, pericarditis, decreased LVEF		

Table 1 continued

Drug class/ agent	Molecular target(s)*	Therapeutic indication(s)	Cardiovascular toxicities with relevant frequency#	Other toxicities of important clinical impact	Recommendations/advices
Sunitinib	**VEGFR1/2/**, **c-KIT**, **PDGFRα/β**, RET, CSF-1R, FLT3, hERG	MRCC, resistant GIST, NETs	Warnings for hypertension, cardiac dysfunction, QT prolongation, venous and arterial thromboembolic events Uncommon: CHF, LV insufficiency Rare: QT prolongation, torsades de pointes Unknown: cardiomyopathy, pericardial effusion	Dermatologic toxicity (hand and foot syndrome) Gastrointestinal toxicity (with pancreatitis) Endocrine toxicity (hypothyroidism) Hepatotoxicity Hematological toxicity (neutropenia, and anemia) Drug interactions (CYP3A4) Osteonecrosis of the jaw (with biphosphonates)	Intense monitoring of blood pressure and proteinuria. Consider referral to (a) hypertension specialist, if hypertension occurs and antihypertensive therapy is insufficient or (b) nephrologist, if abnormal urinalysis with proteinuria Monitoring thyroid and liver function, blood cells count, especially during therapy Electrocardiogram monitoring at regular intervals (before and during treatment) and attention to electrolyte imbalance (especially hypokalemia and hypomagnesemia) Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice)
Sorafenib	**RAF**, **VEGFR2/3**, **PDGFRα/β**, **c-KIT**, FLT3	Resistant RCC, unresectable HCC	Warnings for hypertension, cardiac ischemia/ infarction Highly common: hemorrhage (including gastrointestinal, respiratory and CNS), hypertension Uncommon: hypertensive crisis, CHF	Hepatotoxicity Hematological toxicity (neutropenia, and anemia) Drug interactions (CYP3A4 UGT1A1 e UGT1A9, P-gp)	Intense monitoring of blood pressure and proteinuria. Consider referral to (a) hypertension specialist, if hypertension occurs and antihypertensive therapy is insufficient or (b) nephrologist, if abnormal urinalysis with proteinuria Monitoring liver function, blood cells count, especially during therapy Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice) and of UGT1A1 (e.g., irinotecan)
mAb					
Trastuzumab	**HER2** (ERBB2)	HER2-positive breast cancer, HER2-positive gastric cancer	Warnings for cardiotoxicity Highly common: hypo/hypertension, irregular cardiac beats, palpitations, cardiac flutter Common: CHF, supraventricular tachycardia, cardiomyopathy, decreased LVEF Uncommon: pericardial effusion Unknown: cardiogenic shock, pericarditis, bradycardia	Hypersensitivity reactions (especially during the infusion) Pulmonary toxicity Hematological toxicity (neutropenia)	See specific management of cardiotoxicity in the text

Table 1 continued

Drug class/ agent	Molecular target(s)*	Therapeutic indication(s)	Cardiovascular toxicities with relevant frequency#	Other toxicities of important clinical impact	Recommendations/advices
Bevacizumab	**VEGFR**	Metastatic colorectal cancer, NSCLC, metastatic HER2-negative breast cancer, metastatic RCC†	Warnings for hypertension, proteinuria, venous and arterial thromboembolism, pulmonary hemorrhage, CHF Highly common: hypertension (with hypertensive crisis) Common: CHF, supraventricular tachycardia, hemorrhage, venous and arterial thromboembolism Very rare: hypertensive encephalopathy and posterior leukoencephalopathy syndrome Unknown: thrombotic renal microangiopathy	Hepatotoxicity Gastrointestinal perforation (infrequent but potentially fatal) Hematological toxicity (neutropenia, and anemia) Hypersensitivity reactions	Intense monitoring of blood pressure and proteinuria. Consider referral to (a) hypertension specialist, if hypertension occurs and antihypertensive therapy is insufficient or (b) nephrologist, if abnormal urinalysis with proteinuria
Antiestrogens					
Tamoxifen	**ER**	Breast cancer	Highly common: flush Common: venous and arterial thromboembolic events	Reproductive toxicity Hematological toxicity (thrombocytopenia) Drug interactions (CYP3A4 and 2D6)	Avoid use in pregnancy Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice) Caution when administering SSRIs (e.g., paroxetine)
Drugs with a conditional risk (*i.e., lack of published evidence or uncertain data*)					
TKI					
Lapatinib	**HER2** (ERBB2) EGFR (ERBB1)	Metastatic HER2 positive breast cancer	Warnings for QT prolongation and decreased LVEF Highly common: flush Common: decreased LVEF, QT prolongation	Drug interactions (CYP3A4) Gastrointestinal toxicity	Electrocardiogram monitoring at regular intervals (before and during treatment) and attention to electrolyte imbalance (especially hypokalemia and hypomagnesemia) Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice)
Gefitinib	**EGFR** (ERBB1)	NSCLC	Common: hemorrhage	Pulmonary toxicity (interstitial disease) Hepatotoxicity Drug interactions (CYP3A4)	Vigilance to respiratory symptoms such as cough, dyspnea and fever Monitoring liver function Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice)
Erlotinib	**EGFR** (ERBB1)	NSCLC, PC	No specific mention	Pulmonary toxicity (interstitial disease) Hepatotoxicity Drug interactions (CYP1A1, 3A4, 2C8)	Vigilance to respiratory symptoms such as cough, dyspnea and fever Monitoring liver function Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice)

Table 1 continued

Drug class/ agent	Molecular target(s)*	Therapeutic indication(s)	Cardiovascular toxicities with relevant frequency#	Other toxicities of important clinical impact	Recommendations/advices
Pazopanib	**VEGFR1/2/3**, **PDGFRα/β**, **KIT**	RCC	Warnings for arterial thromboembolic events, hypertension, QT prolongation Common: hypertension Uncommon: QT prolongation, torsades de pointes, chest pain	Hepatotoxicity (especially with pazopanib) Dermatologic toxicity (hand and foot syndrome, photosensitivity) Endocrine toxicity (hypothyroidism, electrolyte and glucose imbalances) Hematological toxicity (neutropenia, thrombocytopenia)	Monitoring thyroid and liver function, as well as electrolytes Intense monitoring of blood pressure and proteinuria. Consider referral to (a) hypertension specialist, if hypertension occurs and antihypertensive therapy is insufficient or (b) nephrologist, if abnormal urinalysis with proteinuria Electrocardiogram monitoring at regular intervals (before and during treatment) and attention to electrolyte imbalance (especially hypokalemia and hypomagnesemia)
Vandetanib‡	**EGFR**, **VEGFR**, RET	MTC	Warnings for QT prolongation and torsades de pointes, heart failure, hypertension Hypertension (incidence: all grades, 33%) QT prolongation (incidence 14%) Heart failure (incidence 0.9%)		
Temsirolimus	**mTOR**	MRCC	Common: hypertension, thromboembolism Uncommon: pericardial effusion	Hypersensitivity reactions (especially during infusion) Infections Pulmonary toxicity (pneumonitis) Metabolic toxicity (hyperlipidemia, hyperglycemia, hypercolesterolemia) Drug interactions CYP3A4	Intense monitoring of blood pressure and proteinuria. Consider referral to (a) hypertension specialist, if hypertension occurs and antihypertensive therapy is insufficient or (b) nephrologist, if abnormal urinalysis with proteinuria Vigilance to respiratory symptoms such as cough, dyspnea and fever Monitoring electrolytes and lipid plasma levels Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin and grapefruit juice)
Everolimus	**mTOR**	MRCC, NETs	Common: hypertension Uncommon: CHF	Hypersensitivity reactions (especially during infusion) Infections Pulmonary toxicity (pneumonitis) Metabolic toxicity (hyperlipidemia, hyperglycemia, hypercholesterolemia) Drug interactions CYP3A4	

Table 1 continued

Drug class/ agent	Molecular target(s)*	Therapeutic indication(s)	Cardiovascular toxicities with relevant frequency#	Other toxicities of important clinical impact	Recommendations/advices
mAb					
Cetuximab	**EGFR** (ERBB1)	Metastatic colorectal cancer, head and neck cancer	Warnings for potential cardiovascular events Uncommon: venous thrombosis	Hypersensitivity reactions (especially during infusion) Dermatological toxicity Pulmonary toxicity Endocrine toxicity (hypomagnesemia)	Close monitoring for neurological signs or symptoms Attention during initial administration Vigilance to respiratory symptoms such as cough, dyspnea and fever
Panitumumab	**EGFR** (ERBB1)	Colorectal cancer	Common: tachycardia Uncommon: hypo/hypertension, flush, cyanosis	Dermatological toxicity Pulmonary toxicity Endocrine toxicity (hypomagnesemia)	Vigilance to respiratory symptoms such as cough, dyspnea and fever
Rituximab	**CD20**	BL	Common: myocardial infarction, atrial fibrillation, tachycardia, hypo/hypertension Uncommon: LV dysfunction, ventricular tachycardia, supraventricular tachycardia, angina, myocardial ischemia Unknown: CHF, vasculitis	Progressive multifocal leukoencephalopathy Hypersensitivity reactions (especially during infusion) Infections	Close monitoring for neurological signs or symptoms Attention during initial administration
Alemtuzumab	**CD52**	Resistant B-CLL	Highly common: hypotension Common: cyanosis, brady/tachycardia, hypertension, vasospasm, flush Uncommon: cardiac arrest, myocardial infarction, peripheral ischemia, angina, atrial fibrillation, extrasystoles, supraventricular arrhythmia Unknown: CHF, cardiomyopathy, decreased LVEF	Progressive multifocal leukoencephalopathy Hypersensitivity reactions (especially during infusion) Infections	Attention during initial administration
Proteasome inhibitors					
Bortezomib	**26S**	Multiple myeloma Mantle cell lymphoma	Warnings for hypotension and CHF Common: hypotension (orthostatic and postural) Uncommon: cardiac arrest, cardiogenic shock, myocardial infarction, angina, CHF, pulmonary oedema, A-V block, tachycardia, atrial fibrillation, vasculitis, cerebral hemorrhage Unknown: cardiac tamponade, pericarditis	Hematological toxicity (thrombocytopenia, neutropenia, anemia) Neurotoxicity (peripheral neuropathy) Pulmonary toxicity (ARDS)	Monitor complete blood counts and platelet count Monitor patients for symptoms of peripheral neuropathy (e.g., burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness) Vigilance to respiratory symptoms such as cough, dyspnea and fever

Table 1 continued

Drug class/ agent	Molecular target(s)*	Therapeutic indication(s)	Cardiovascular toxicities with relevant frequency#	Other toxicities of important clinical impact	Recommendations/advices
Histone deacetylase inhibitors					
Vorinostat‡	**HDAC**1, 2, 3, 6	Primary cutaneous T-cell lymphoma	Warnings for QT prolongation and thromboembolism QT prolongation (incidence: 3.5–6%) Peripheral oedema (incidence: 12.8%)	Hematological toxicity (thrombocytopenia) Renal toxicity	Monitoring blood cell counts and creatinine

Therapeutic target(s) are highlighted in bold

ARDS acute respiratory distress syndrome, *B-CLL* B-cell chronic lymphocytic leukemia, *BL* B-cell lymphoma, *CEL* chronic eosinophilic leukemia, *CHF* congestive heart failure, *CML* chronic myeloid leukemia, *CMML* chronic myelomonocytic leukemia, *ER* estrogen receptors, *FDA* Food and Drug Administration, *GIST* gastrointestinal stromal tumor, *HCC* hepatocellular carcinoma, *LVD* left ventricular dysfunction, *MRCC* metastatic renal cell carcinoma, *NSCLC* non-small-cell lung cancer, *MTC* medullary thyroid carcinoma, *NETs* pancreatic neuroendocrine tumors, *PC* pancreatic cancer, Ph^+ *B-ALL* Philadelphia chromosome positive B-cell acute lymphoblastic leukemia, *SD* sudden death, *TdP* torsades de pointes, *ABL* Abelson tyrosine kinase, *CSF1R* colony-stimulating factor 1 receptor, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *hERG* human ether a-go-go related gene, *FLT3* FMS-related tyrosine kinase, *mTOR* inhibitor of mammalian target of rapamycin, *NRTK* nonreceptor tyrosine kinase, *PDGFR* platelet-derived growth factor receptor, *RAF* serine/threonine-protein kinase-transforming protein, *RET* rearranged during transfection, *VEGFR* vascular endothelial growth factor receptor

Data from the current Italian Summary of Product Characteristic (SPC, Sect. 4.8: side effects from clinical and post-marketing studies). If multiple SPCs were available (e.g., for different formulations), priority was given to the parenteral route (i.v. > i.m > s.c.) or to the highest dose

† All therapeutic indications are in combination therapy

‡ Because the Italian SPC is currently not available, the DRUGDEX® Drug Summary Information (http://www.thomsonhc.com, last accessed July 12, 2011) was used to retrieve information

toxicologists to identify the cause of cardiotoxicity and turn promiscuous drugs into safer agents [9].

Because of this complex scenario, chemotherapy-related cardiotoxicity should be viewed as a multifaceted issue requiring a multidisciplinary approach to properly manage and monitor patients. Recently, the novel discipline of cardio-oncology has been advocated in clinical practice as a pharmacology-oriented translational approach that should bring together heterogeneous areas [10, 11]. Pharmacologists, toxicologists, internists and primary care physicians should join cardio-oncologists and combine efforts to ensure a holistic oncological support: in this context, the International CardiOncology Society has been created (http://www.cardioncology.it/).

Emerging cardiovascular toxicities of targeted therapy

Hypertension

Magnitude of the problem

Increased BP can be considered as an expected dose-dependent side effect of several anti-angiogenesis drugs and reflects the inhibition of vascular endothelial growth factor (VEGFR) [12]. Therefore, the occurrence of hypertension in cancer patients treated with anti-VEGF targeted agents has been thought as a surrogate biomarker of anti-cancer drug efficacy. On the other hand, hypertension can be life-threatening (malignant hypertension) and cause systemic damage such as neurological complications, namely the reversible posterior leukoencephalopathy syndrome.

The incidence and severity of hypertension depend on the drug regimen and underlying coexisting diseases. Recent meta-analyses assessed the overall incidence of hypertension with angiogenesis inhibitors. For sunitinib, calculated incidence are 21.6 and 6.8% for all-grade and high-grade hypertension, with relative risks (RR) of 3.44 and 22.72, respectively [13]. Similar results are reported for sorafenib, with a RR of 6.11 in patients with renal cell carcinoma (RCC) [14]. As regards bevacizumab, Ranpura et al. [15] find high-grade hypertension in 7.9% of patients, without significant difference between high dose and low dose.

These epidemiological data are probably underestimated for several reasons: different classifications, definitions and exclusion criteria among trials, exclusion of patients with poorly controlled hypertension and unrealistic routine monitoring outside the hospital setting. Moreover, the Common Terminology Criteria for Adverse Events (CTCAE) terminology have been implemented over the years, changing criteria to diagnose and grade hypertension

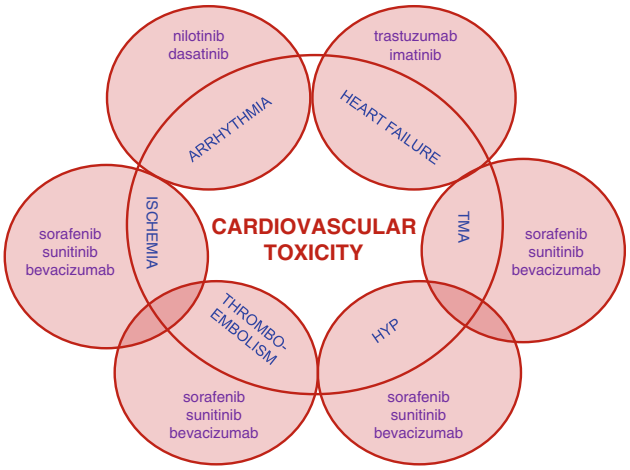


Fig. 1 Spectrum of cardiotoxicities associated with anticancer-targeted therapy. Several targeted drugs used in oncology have detrimental impact on cardiovascular physiology through on-target or off-target effects. Note that (1) the same drug may be associated with different cardiotoxicities; (2) overlaps exist among side effects because of common pathogenesis (e.g., thromboembolism and ischemia); (3) areas of circles and overlaps are not necessarily proportional to the magnitude of the problem in clinical practice. *HYP* hypertension, *TMA* thrombotic microangiopathy

in novel trials. A recent retrospective study by Chu et al. [16] reports an incidence of 47% for sunitinib. The incidence can also vary according to tumor type, being higher in RCC than in hepatocellular carcinoma (HCC) and gastrointestinal stromal tumor (GIST), for sorafenib and sunitinib, respectively. Finally, the incidence appears to increase in parallel with the degree of angiogenesis inhibition: 67% with combined bevacizumab and sorafenib, 92% with combined bevacizumab and sunitinib [17, 18].

Mechanistic basis

Control of BP can be achieved through different mechanisms. Among these, decreased nitric oxide (NO) bioavailability is thought to play a pivotal role [19]. Because endothelial NO synthase is up-regulated by VEGF, inhibition of VEGF will decrease NO production and prostacyclin activity by endothelial cells, which may account for increased vascular resistance. Another hypothesis suggests the contribution of vascular rarefaction, i.e., a functional (decreased microvessels perfusion) or structural (reduced capillary density) depletion of microvascular endothelial cells. This second mechanisms does not appear to play an important etiological role, at least in the initial phase of angiogenesis inhibition, because hypertension occurs shortly after drug administration (within hours) and is rapidly reversed after treatment discontinuation. Results by Veronese et al. [20] support vascular stiffness as an important factor in the genesis of hypertension by showing no correlation between BP and plasma levels of renin–angiotensin–aldosterone system. Because VEGF signaling is an important factor in glomerular physiology, renal toxicity (namely proteinuria) has been associated with hypertension, especially in patients treated with bevacizumab (up to 41–63%) [21]. This relationship is dose-dependent and appears to be causal, as proteinuria diminishes or disappears after reduction or discontinuation of therapy. Typical pathological abnormalities are referred to as glomerular thrombotic microangiopathy (TMA).

Handling strategies

The Investigational Drug Steering Committee of the National Cancer Institute convened an interdisciplinary panel to generate a consensus report consisting of five key recommendations in hypertension care [22]. The panel recognized the challenging task of incorporating this tailored approach into routine clinical practice, but also emphasized the importance for the oncologist to work in close collaboration with cardiovascular specialists and general practitioners.

The goal of BP optimization is to allow continuous and safe administration of VEGF-targeted drugs without dose modification. Before considering treatment with VEGF inhibitors, a careful screen of baseline cardiovascular risk is recommended, including repeated BP measurements as per recommended technique. Cardiovascular anamnesis with physical and laboratory investigations are mandatory in risk stratification, as endorsed by the European Society of Hypertension and the European Society of Cardiology. Because the underlying glomerular disease or TMA can be responsible for de novo or worsening hypertension, it is important to evaluate renal function and quantify potential proteinuria deserving specific referral to nephrologists [23]. The purpose of this initial assessment is not to exclude patients from effective therapy, but rather to provide baseline patient risk level, on which rigorous surveillance should be started. It is important to maintain or start antihypertensive therapy with the BP goal of <140/90 mmHg. These thresholds should be adjusted according to associated co-morbidities (e.g., <130/80 mmHg in patients with diabetes or chronic kidney disease).

A variety of medications, including diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and calcium channel blockers, have been used to treat hypertension in oncological patients. All these agents are effective on an individual patient basis, with no studies documenting superiority of a given drug [24]. Therefore, the selection of the most appropriate drug should be based on (1) pharmacokinetic aspects; (2) cancer-related factors; (3) specific cautions and contraindications related to the drug and co-

morbidities and patient's needs. For instance, ACEI are a logical choice in diabetic patients due to the positive effect on the underlying proteinuria. Moreover, they act rapidly, as compared to dihydropyridine calcium channel blockers. Caution is needed in using non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, which are also CYP 3A4 inhibitors. Because endothelial NO is considered as a putative mediator in the pathogenesis, agents acting by increasing NO such as nitrates or nebivolol have been proposed as add-on treatment in case of uncontrolled BP [24].

Once on therapy, regular monitoring is recommended weekly during the first cycle of therapy, and then at least every 2 or 3 weeks for the duration of drug regimen. This frequency should be adjusted according, for instance, to concomitant agents increasing the risk of hypertension (e.g., antinflammatory drugs, erythropoietins, contraceptives). In case of systolic BP >200 mmHg or diastolic BP >100 mmHg discontinuation or, where appropriate, dose reduction, must be considered. Reasonable efforts should be oriented to maintain a patient at the highest tolerable dose by referral to a hypertension specialist in case of uncontrolled hypertension. BP measurement may be carried out either with home BP or office nursing monitoring on a regular basis, especially during the first week of treatment because the magnitude of BP elevation is unpredictable [22]. Home monitoring entails a higher degree of patient education and training, but it provides the patient with the opportunity to actively participate in self management.

In summary, because hypertension is an established side effect of angiogenesis inhibitors and can occur at anytime after therapy initiation, clinicians must be aware of this issue and add periodic BP monitoring to standard medical care.

Left ventricular dysfunction and heart failure

Challenging diagnosis

The diagnosis of HF in patients with cancer needs great clinical experience, and remains subject to high inter-observer variability [25]. Particular attention should be paid to subtle signs and symptoms such as minor impairment of physical exercise and tachycardia at rest. Dyspnoea is mostly under-diagnosed in patients undertaking chemotherapy [26]. Moreover, recognizing drug-induced HF is complicated by an underlying cancer cachexia mimicking dyspnoea, peripheral edema and fatigue. In this context, the assessment of LVEF has become the most common screening method for cardiotoxic effect. This parameter is highly imprecise, especially due to potential underestimation of cardiac damage. Currently, several conventional and promising methods for early detection of subclinical cardiotoxicity are available [27]. Because none of these diagnostic tools represents the gold standard, the use of different methods represents the best option for appropriate management. At present, a series of considerations on costs and feasibility suggest that echocardiography (ECHO) or ventriculography multiple-gated acquisition (MUGA) scan play an important role for cardiac monitoring. This non-invasive technique can be performed at bedside, easily repeated and allows the assessment of changes in systolic and diastolic function, as well as ruling out pericardial effusion and pulmonary hypertension. However, inter- and intra-observer variability during serial measurements of LVEF should be taken into account. The most important drawback pertains to the identification of cardiac damage only when functional impairment has occurred. Therefore, novel echocardiographic methods are under investigation and appear promising in assessing cardiac morphology and function. For instance, tissue Doppler imaging may implement ECHO by detecting subclinical markers of cardiac dysfunction (e.g., Tei index). This parameter represents a validated index providing a functional evaluation of the ventricle (systolic and diastolic). Markers of the underlying diastolic function [e.g., deformation (strain) and deformation rate (strain rate) of ventricular walls] are also under investigation for early detection of chemotherapy-related cardiotoxicity. Stress ECHO is a further technique that is receiving interest as it can assess the contractile myocardium reserve. Recently, Walker et al. [28] tested the accuracy of conventional ECHO and MUGA in comparison with three-dimensional (3-D) ECHO and cardiac magnetic resonance imaging. In a breast cancer population receiving adjuvant trastuzumab and an anthracycline, 3-D ECHO is as accurate as conventional methods for LVEF measurement. Finally, cardio-specific biomarkers have been proposed for early detection, assessment and monitoring of cardiotoxicity (see below) [29].

Molecular mechanisms

Although each anticancer agent causes cardiotoxicity through inhibition of specific targets, two major molecular mechanisms have been described: the "on-target" and "off-target" toxicity [30]. The on-target effect (also known as mechanism-based) is caused by a target promoting both cancer cell growth and cardiomyocyte function. A classical example is trastuzumab. The off-target effect, instead, occurs when a TKI causes inhibition of a "bystander" target (i.e., a target not essential to kill cancer cells but involved in cardiomyocyte survival), and is inherently related to the restricted target selectivity. From a molecular standpoint, TKIs are classified according to the selectivity for their targets. However, with few exceptions, most of

marketed TKIs act by regulating several kinases, which may be responsible not only for therapeutic affect, but also for cardiotoxicity. The recent in vitro study by Hasinoff and Patel [31] demonstrates that myocyte damage is correlated with a lack of target selectivity, thus suggesting the multifactorial nature of cardiac dysfunction.

An important clinical classification distinguishes between type I and II cardiotoxicity, depending on the reversibility of the damage. In contrast to anthracycline cardiotoxicity, which is irreversible, cumulative (i.e., dose-dependent) and associated with ultrastructural changes of necrosis, trastuzumab-associated cardiac dysfunction is thought to be idiosyncratic, and at least partially reversible since no structural damage has been detected by myocardial biopsies of patients [32]. Although reversibility of type II agents has been called into question [33], this form of "hibernation" with loss of contractility could be also considered for TKIs.

HER2-targeted agents

Trastuzumab, the first targeted agents approved in 1998 for metastatic breast cancer, is a humanized mAb targeted against the extracellular domain of the human epidermal growth factor receptor 2 (HER2, also known as ERBB2), which is over-expressed in 20% of breast cancers. Landmark adjuvant studies demonstrate that trastuzumab, either alone or in combination with chemotherapy, reduces the risk of death by 33% in women with HER2-positive early breast cancer [34]. Although pre-clinical studies did not reveal any cardiac toxicity, the first phase III pivotal trial reports significant cardiac dysfunction in combination therapies (8% in patients receiving an anthracycline and cyclophosphamide alone, 13% in those receiving paclitaxel and trastuzumab, 27% in recipients of anthracycline plus cyclophosphamide and trastuzumab) [35]. As a result, the concomitant use with anthracyclines was abandoned in metastatic breast cancer patients, and subsequent adjuvant trials were designed with regular cardiac monitoring. Although data mining and across-trial comparisons are problematic (differences in patient populations, chemotherapy regimens, monitoring schedules and sequencing of treatments), these studies suggest that cardiac dysfunction is idiosyncratic, reversible (at least partially) and often manifested as an asymptomatic decline in LVEF. The overall incidence in the literature shows a wide range of variation, depending on different trastuzumab-containing regimens and on studied outcomes, being higher in patients receiving anthracyclines (with sequential therapy safer as compared to concurrent administration) [36].

An important clinical aspect of trastuzumab-related cardiotoxicity is the almost complete recovery after discontinuation with (generally) well tolerated re-challenge [37]. Reversibility and benign course have been further substantiated by two independent reviews of large prospective trials [38]. The pathophysiology of cardiotoxicity related to trastuzumab is highly complex and still unclear, but disruption of the HER2 signaling cascade within the heart is thought to play a major role by activating the mitochondrial apoptotic pathway [2]. In particular, the neuregulin 1/ErbB signaling is implicated in cardiac development and survival, both in healthy and pathological setting. These crucial functions in promoting cardiac repair have important therapeutic implications. Additional mechanisms have been proposed, which may involve a unique intracellular signaling response of cardiomyocytes to HER2 or the antibody-dependent cell-mediated cytotoxicity effect of trastuzumab [2]. It should be investigated whether or not this immune-mediated effect is of relevance for other agents interfering with HER2. Preliminary analysis on pertuzumab, a HER2 dimerization inhibitor, recorded an asymptomatic ventricular dysfunction in 6.5% of patients, with symptomatic CHF occurring in 0.3%. Notably, no cardiotoxic synergism was noted in combination regimens [39].

Current research is gaining insight into the inherent cardiotoxicity of trastuzumab by analyzing the interaction with anthracyclines. Although an intrinsic degree of cardiotoxicity should be recognized, this risk is remarkably higher when combined with anthracyclines. It appears that, at the current state of knowledge, trastuzumab has a low inherent capacity to cause myocyte death, but a far greater potential to amplify anthracycline toxicity by impairing cell repair [40]. Therefore, late-onset cardiac toxicity remains a potential issue and support long-term surveillance of patients undertaking combination therapy.

In the wake of the experience with trastuzumab, prospective evaluation of cardiac function was mandatory during early phases of drug development for lapatinib, an orally available dual kinase inhibitor of epidermal growth factor receptor (EGFR) and ERBB2, but failed to detect significant cardiotoxicity. Revision of 44 clinical studies enrolling 3,689 patients receiving lapatinib reveals a 0.2% rate of symptomatic CHF and a 1.4% rate of asymptomatic cardiac events [41]. Therefore, despite heterogeneity among patients, lapatinib appears considerably less cardiotoxic than trastuzumab. Interestingly, the off-target effect on the cytoprotective AMP-activated protein kinase (AMPK) in cardiomyocytes may at least partially counteract cardiac dysfunction associated with HER2 inhibition, and explain the relatively safer cardiac profile of lapatinib [42]. The issue of long-term cardiotoxicity must be timely addressed, because lapatinib may theoretically represent first-line treatment in patients with HER2-positive breast cancer.

VEGF-targeted agents

Bevacizumab, a recombinant humanized mAb against vascular endothelial growth factor (VEGF) receptor, has proven efficacy in several forms of tumors, including metastatic breast, colorectal, renal and small-cell lung cancer. However, the FDA has recently proposed to remove the indication in metastatic breast cancer after potentially serious side effects were reviewed, including heart attack and failure [43]. In addition, in a recent meta-analysis, the use of bevacizumab in combination with chemotherapy is associated with an increased risk of fatal adverse events, as compared to chemotherapy alone (RR = 1.46 6), especially in patients receiving taxanes or platinum agents (RR = 3.49) [44]. The meta-analysis by Choueiri et al. [45] finds in metastatic breast cancer patients an overall incidence of high-grade HF of 1.6% (RR = 4.74). However, several issues remain unclear, and deserve further investigation through individual patient data, especially the aspects related to reversibility and the contribution of other cardiotoxic drugs before bevacizumab administration (e.g., anthracyclines). Pending adjuvant trials will be critical in understanding these topics.

ABL-targeted inhibitors

Imatinib is an inhibitor of the breakpoint cluster region-Abelson (Bcr-Abl) fusion protein (over-expressed in patients with chronic myeloid leukemia), and also inhibits other kinases such as c-Kit and platelet-derived growth factor receptor (PDGFR), which are targets in gastrointestinal stromal tumors (GISTs). It is a typical example used in the literature to describe on-target toxicity [30]. However, the extent and clinical relevance of cardiotoxicity is still under scrutiny with divergent opinions. The original observation by Kerkela et al. [46] reports modest, but consistent, decline in LVEF, with contractile dysfunction and cellular abnormalities suggestive of a toxic myopathy. As a response, Novartis retrospectively reviewed 6 registration trial data of 2,327 patients and reports a CHF incidence of 0.5% [47]. Similarly, Atallah et al. [48] report a CHF incidence of 1.7%. It should be acknowledged that most patients suffered from co-morbidities predisposing to CHF (e.g., hypertension, diabetes). A prospective cross-sectional study on 160 patients finds no statistical difference among groups in terms of clinical and laboratory findings, with only one case of depressed LVEF [49]. A recent prospective cardiac assessment of 59 patients reports no evidence of myocardial deterioration at baseline and after 12 months of therapy [50]. The independent multicenter Imatinib Long Term Effects (ILTE) study suggests that long-term adverse events appear modest (only 2.3% discontinued imatinib due to toxic effects) with no difference in overall survival as compared to general population [51]. The inhibition of Bcr-Abl with endoplasmic reticulum stress was found to play a key role in imatinib-induced cardiac injury. Indeed, a redesigned variant of imatinib with no longer Abl-inhibition shows reduced cardiotoxicity in GIST patients [9]. At the current state of knowledge, cardiotoxicity associated with imatinib appears a manageable clinical issue occurring in susceptible individuals with predisposing factors. This minor cardiac complication should not limit its therapeutic use, and does not justify drug discontinuation in patients requiring long-term treatment.

As regards dasatinib and nilotinib, scarce published literature exists. Yeh and Bickford [52] report that the incidence of CHF ranges from 2 to 4%. For these drugs, the risk of QT prolongation is a more important type of cardiotoxicity. Because dasatinib and nilotinib are approved as second-line TKIs in case of insufficient imatinib response, there is concern on cumulative cardiotoxicity. Recently, a warning was issued by the Italian Regulatory Agency (AIFA), in accordance with the European Medicines Agency and Bristol-Myers Squibb, on the risk of pulmonary arterial hypertension associated with dasatinib [53], with recommendations on the need for clinical and echocardiographic monitoring (see Table 1). For nilotinib, severe peripheral artery disease and other arteriopathies have been retrospectively documented in a significant proportion (6.15%) of patients [54].

Multikinase inhibitors

Sunitinib and sorafenib are usually referred to as multikinase inhibitors that, besides VEGF, also target PDGF and c-KIT. The precise molecular mechanism involved in cardiotoxicity is uncertain. It has been hypothesized that sunitinib cardiotoxicity could be mediated through inhibition of AMPK, although hypertension is considered a major contributor to the cardiac deterioration [2]. It is also possible that inhibition of PDGF in the heart play a role, as this signaling pathway has been recently associated with a cardioprotective effect [55]. Schmidinger et al. [56] estimate an incidence of LVEF drop of 5% for sorafenib and 14% for sunitinib. Concerning sunitinib, two retrospective reviews record class II to IV CHF in 8% and 15% of patients, respectively [16, 57]. Notably, another investigation describes a cardiotoxicity that results in a substantial morbidity and, in some cases, mortality [58]. The only partial recovery suggests that cardiotoxicity may represent a potentially serious concern for sunitinib, and underscores the need for careful monitoring. Particular attention should be paid when patients are sequentially treated with sunitinib and sorafenib, as additive cardiotoxicity has been reported [59].

Other targeted agents

Because of the critical role of kinases in tumorigenesis and overlaps with signaling pathways driving cardiomyocyte survival, a number of potential targets resulting in cardiotoxicity are expected [30]. Several lines of evidence drew the attention to EGFR, the JAK/STAT and P13K/Akt pathways, which ultimately converge on mTOR, a central regulator of cardiomyocytes growth. Pleiotropic effects and similarity between cancer and cardiac signaling raise some concern on the risk of cardiotoxicity of agents targeting these pathways, thus deserving vigilance.

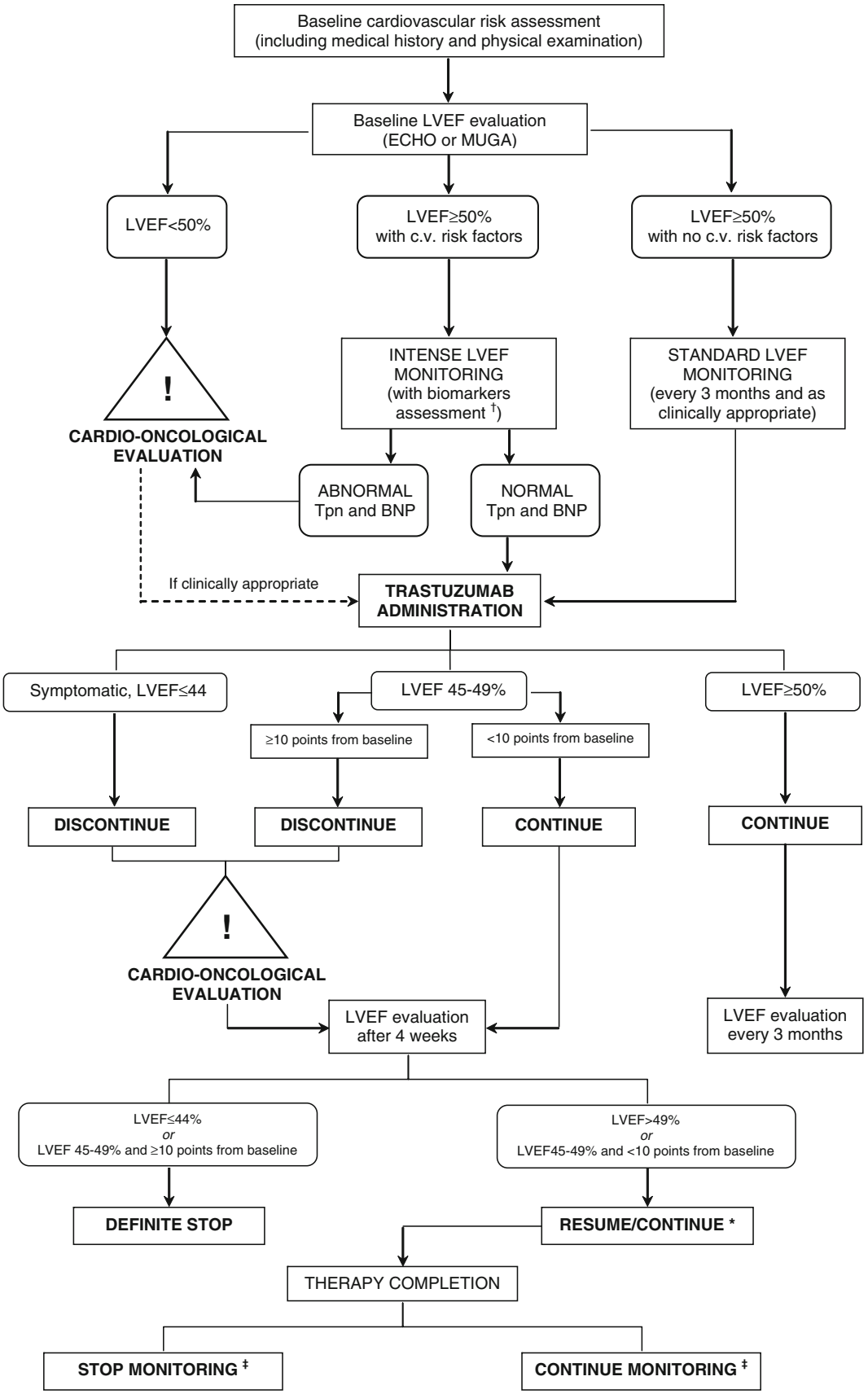
Management

Several strategies have been proposed to deal with cardiotoxicity, both during drug development and in clinical practice. Concerning pre-clinical phase, a rational drug redesign has been successfully demonstrated for imatinib and sunitinib to avoid cardiac injury while maintaining antitumor activity. Recently, Fernandez and Sessel [60] propose, at a conceptual level, "therapeutic editing" to reduce side effects. The editor is defined as a drug capable of exerting selective antagonism in "off-target" cells (i.e., myocytes), thus suppressing the adverse effect caused by the primary drug. Both editor and primary drug overlap in "on-target" cells (i.e., tumor cells), thus acting synergistically. Nanotechnology and bioengineering approaches such as target delivery of drugs specifically to malignant cells are also under implementation. While at present the hypothesis of profiling the kinase selectivity to predict cardiotoxicity appears much more theoretical than real, the use of liposomal, polymer drug-conjugate and micellar formulations is a clinical praxis with promising results [61]. As regards clinical practice, there are no specific guidelines for cancer patients, although a number of recommendations have been proposed to manage cardiotoxicity, especially for trastuzumab in early breast cancer [62]. Consensus is needed on the appropriate monitoring upon completion of therapy. Because there is no evidence of LVEF deterioration in patients who had no reduction during treatment, stop monitoring should be considered provided that no changes in LVEF and symptoms. The leading concept in managing cardiac dysfunction related to trastuzumab is the active role of individual patient care decisions to maximize cancer treatment benefit while minimizing cardiovascular risk. Figure 2 provides a synopsis of patient management in the adjuvant setting, based on a multidisciplinary proactive approach involving cardiologists and oncologists. Teamwork is of paramount importance and should be strengthened for new targeted agents to support favorable clinical outcome. An important aspect of this interdisciplinary collaboration pertains the importance of cardiovascular screening to plan appropriate monitoring according to individual risk level. Schmidinger et al. [56] observe that careful monitoring is justified to detect early signs of myocardial damage. In addition, cardio-oncological chemoprevention through diet-derived phytochemicals is emerging as a promising approach to mitigate cancer, cardiovascular disease and even drug-induced cardiotoxicity [63].

The role of risk factors warrants ad hoc investigation, especially for TKIs. As regards trastuzumab, several host- and drug-related factors have been related to an increased risk of cardiotoxicity: age >50 years, borderline LVEF, history of cardiovascular diseases and prior anthracyclines administration, with sequential therapy safer than concurrent regimen. Concerning TKIs, a history of CHF and/or coronary artery disease were the only risk factors associated with sunitinib [57].

Evidence and experience have begun to accrue on the emerging role of biomarkers not only in diagnosis, but also in the management of cardiac dysfunction induced by anticancer drugs. This approach is minimally invasive, less expensive with no radiation for patients and no dependence on technical skills as compared to imaging techniques. Major limitation pertains to the need to collect blood samples at several time periods due to unpredictable troponin release kinetics and the undefined timing of sampling to maximize sensitivity and specificity. Commendable investigations by Cardinale and coworkers [64–66] in the past decade underline the role of troponin I (TnI) as a qualitative and quantitative biomarker in selecting high-risk patients on whom to perform stringent surveillance and plan preventive strategies to improve clinical outcome. Other biomarkers such as B-type natriuretic peptide (BNP) and the amino-terminal fragment of its precursor (NT-proBNP) are promising to diagnose subclinical damage. Further prospective studies are needed to clarify whether TnI or other biomarkers should be routinely incorporated in clinical practice. The most intriguing and challenging application of these biomarkers is the use of pharmacological therapy in selected high-risk patients (i.e., those with a high probability of symptomatic heart failure because of biomarker increase during chemotherapy), with the aim of interfering with the natural history of cardiotoxicity. The experience of the European Institute of Oncology demonstrates that the use of enalapril in patients with TnI increase after chemotherapy reduces the incidence of cardiac events as compared to controls (2 vs. 52%), especially in patients with persistent TnI elevation [67].

Once pharmacological treatment is required, patients should be managed with standard pharmacological armamentarium: diuretics, ACEI (or ARB) and beta-blockers. The choice and combination of agents should be based on


Baseline cardiovascular risk assessment
(including medical history and physical examination)
Baseline LVEF evaluation
(ECHO or MUGA)
LVEF<50%
LVEF≥50%
with c.v. risk factors
LVEF≥50%
with no c.v. risk factors
!
CARDIO-ONCOLOGICAL
EVALUATION
INTENSE LVEF
MONITORING
(with biomarkers
assessment †)
STANDARD LVEF
MONITORING
(every 3 months and as
clinically appropriate)
ABNORMAL
Tpn and BNP
NORMAL
Tpn and BNP
If clinically appropriate
TRASTUZUMAB
ADMINISTRATION
Symptomatic, LVEF≤44
LVEF 45-49%
LVEF≥50%
≥10 points from baseline
<10 points from baseline
DISCONTINUE
DISCONTINUE
CONTINUE
CONTINUE
!
CARDIO-ONCOLOGICAL
EVALUATION
LVEF evaluation
after 4 weeks
LVEF evaluation
every 3 months
LVEF≤44%
or
LVEF 45-49% and ≥10 points from baseline
LVEF>49%
or
LVEF45-49% and <10 points from baseline
DEFINITE STOP
RESUME/CONTINUE *
THERAPY COMPLETION
STOP MONITORING ‡
CONTINUE MONITORING ‡

◀ **Fig. 2** Proposed algorithm for accurate monitoring of cardiac safety in the adjuvant setting of patients with HER2-positive breast cancer. A multidisciplinary approach embracing cardio-oncological expertise is shown. Adapted from Raschi et al. [1] with permission of the copyright holder (Elsevier). The *triangle* with the exclamation mark indicates the need for individual cardio-oncological evaluation on initiating, continuing or resuming trastuzumab. This clinical evaluation considers addition of medical therapy for CHF with LVEF (and possibly biomarker) reassessment. *LVEF* left ventricular ejection fraction, *BNP* brain natriuretic peptide, *CT* chemotherapy, *CHF* chronic heart failure, *Tpn* troponin. *Asterisk* In case treatment is resumed after any discontinuation due to LVEF abnormalities, LVEF should be assessed monthly. *Dagger* there is no consensus on the timing and frequency of monitoring biomarkers, but baseline and serial measurements after each cycle of trastuzumab can be considered. *Double dagger* although the Italian SPC states that LVEF should be monitored every 6 months for 2 years after completion of therapy, there is no evidence that LVEF decreases after treatment completion in patients who did not experienced reduction during therapy. The optimal duration of therapy of CHF is also unclear, especially in the absence of prior anthracycline chemotherapy

clinical judgment, patient's needs and side effects. Early and timely therapy has a positive impact upon cardiac function. Cardinale et al. [68] recently demonstrate that, in patients with anthracycline-induced cardiomyopathy, early treatment with ACEI (and possibly a beta-blocker) allow complete recovery from LVEF. Responders also show a lower rate of cumulative cardiac events. However, it was recently reported that many cancer survivors with asymptomatic decreased LVEF are receiving neither standard treatment nor cardiac specialty consultation [69].

Thromboembolic complications

Incidence and mechanism

Vascular complications, including venous thromboembolism (VTE) or arterial thromboembolism (ATE) and hemorrhage, have emerged as significant toxicities with angiogenesis inhibitors, especially when administered in combination with standard chemotherapy [70]. Because cancer per se increases the risk of these events, the relative contribution of anticancer drugs is currently undefined. Indeed, a recent study of individual patient data states that the risk of VTEs is driven predominantly by tumors and host risk factors [71]. Several meta-analyses and literature review address the incidences of ATE and VTE events with targeted agents [70].

For bevacizumab, the first pooled analysis of 1,745 patients shows an increased risk of ATE (3.8% in treatment arm vs. 1.7% in control arm), but not VTE. Most ATE episodes are myocardial or cerebrovascular events [72]. A subgroup analysis by Schutz et al. [73] finds an overall RR of ATE of 1.46 with no differences on studied outcomes (e.g., types of malignancy, high vs. low dose, early vs. advanced disease). The meta-analysis by Ranpura et al. [74] assesses an incidence of all-grade and high-grade ATE of 3.3 and 2.0%, respectively (RR = 1.44; increased in patients with RCC). Only the risk of high-grade ischemia is significantly higher as compared to controls (RR = 2.14). A systematic review and meta-analysis of 15 trials finds rates of all-grade and high-grade VTE of 11.8 and 6.3%, respectively, with similar increase at 2.5 and 5 mg/kg/week [75].

Concerning sunitinib and sorafenib, few thrombotic complications have been observed, with an overall incidence of less than 10%. Choueiri et al. [76] find an incidence of 1.3 and 1.7%, respectively, with no statistically significant difference. Semaxinib, VEGF-1 and VEGF-2 inhibitor, is a paradigmatic example illustrating the premature termination of a phase I study for unacceptable thrombotic risk. Significant risk was not found for other targeted therapy such as the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and sirolimus.

Predisposition to thrombosis and bleeding after initiation of VEGF-targeted drugs reflects the variety of actions of VEGF on vascular walls and coagulation system. It stimulates endothelial proliferation, survival and integrity by increasing NO and prostacyclin production and maintains blood viscosity via erythropoietin regulation [70].

Management

It is widely accepted that cancer patients have increased VTE risk, and need preventive measures (e.g., during surgical procedures or periods of immobility). The increased risk of VTE or ATE reported in association with antiangiogenic agents suggests the need for thromboprophylaxis in the ambulatory cancer setting. However, the majority of available data refers to the use of thalidomide in multiple myeloma in non-prospective randomized trials. At present, the scant experience is insufficient to recommend routine use of aspirin or anticoagulants, and the benefit of preventing thrombosis should be balanced with the increased risk of hemorrhagic complications [70]. If anticoagulants or antiaggregants are administered, caution is needed, and close monitoring is warranted, so that all emerging toxicities are carefully reported.

Monitoring of therapy and pharmacovigilance: the key to appropriateness

The trastuzumab experience has taught several lessons. First, prospective evaluation of cardiac function should be planned to ensure timely detection of adverse drug reactions (ADRs). Second, the accuracy of pre-clinical models is insufficient to predict cardiovascular risk. Third, a higher than expected incidence is found in patients undergoing combination regimens, especially when other cardiotoxic

agents are concurrently administered. Fourth, long-term cardiac safety and reversibility remain open issues. Although randomized clinical trials represent the highest level of evidence, and do usually have internal validity, small sample size, too-stringent enrollment criteria and short-term follow-up do not allow generalisability and translation into clinical practice. Moreover, safety is rarely tested as a pre-specified endpoint. In this context, onco-vigilance (i.e., pharmacovigilance oriented to oncologic drugs) is an emerging area, which may promote awareness among physicians, thus supporting oncologists and cardiologists in optimizing patient outcomes (i.e., the balance between the risk of cardiotoxicity and the benefits of oncologic therapy). The relatively low predictability of preclinical tests, and the explosion in the number of anticancer drugs in the pipeline makes onco-vigilance an emerging need. Physicians should routinely consider the importance of baseline screening for subclinical cardiovascular manifestations, because prompt treatment appears to prevent the occurrence of late-onset cardiotoxicity [67]. The clinical pharmacologist, indeed, is a key professional figure with translational skills that may ensure close collaboration between toxicologists and cardio-oncologists.

Several toxicities associated with older anticancer agents are frequent and expected, but cannot be prevented (e.g., bone depression, nausea, vomiting, alopecia); the oncologists are usually well aware and report these ADRs during the pre-marketing phase of drug development. However, the encouragement in the reporting of ADRs represent a challenging task to be promoted so that under-reporting is recognized as the main limitation of pharmacovigilance system. It was recently demonstrated that the 39% of serious events associated with targeted anticancer drugs are not reported in pivotal trials, and 49% are not described in the initial drug labels [77]. Surveillance of safety of oncologic drugs is of primary importance, keeping in mind the potential long-term use of these drugs. In addition, the accelerated approval of anticancer drugs initiated by the FDA in 1992 and implemented over years, may theoretically cause the early release of unsafe/ineffective drugs [78]. Earlier access to the market for innovative drugs might be acceptable provided that adequate measures are taken for early detection of safety issues that are not easily found pre-registration. Indeed this is an area to be improved because at present the published literature on pharmacovigilance of oncologic drugs is scant.

The retrospective study by Hauben et al. [79] shows that 18 out of 26 known drug-event associations could have been detected several years before relevant changes in the drug label. Pharmacovigilance aims at early and timely detection of safety issues through different approaches, such as the analysis of spontaneous reporting systems and healthcare databases. We support and encourage a formal, timely and accurate reporting of suspected ADRs (including asymptomatic cardiac dysfunction) to make pharmacovigilance system a reliable indicator of risk to estimate the magnitude of clinically relevant drug-induced events. A standard classification system, namely Medical Dictionary for Regulatory Activities (MedDRA), has been developed to facilitate drug-event reporting and codification. Notably, MedDRA has been even harmonized with the corresponding classification system used in clinical trials (i.e., CTCAE), thus assisting event codification among different sources of data. This proactive surveillance should become integral part of the risk/benefit assessment of medicines and support physicians in proper decision-making.

An emerging aspect of onco-vigilance is the creation of drug- or disease-based registries. While pharmacovigilance is mainly oriented to drug safety, and should effectively promote the appropriate use of medicines, registries are emerging tools for long-term monitoring of drug safety profile, and have the potential to describe the clinical phenotype of patients experiencing cardiotoxicity, identifying susceptible patients. This risk stratification based on patients' characteristics should be viewed in conjunction with the intrinsic risk associated with individual anticancer agents in order to assess the overall risk profile of patient, and to support the most appropriate risk management in the real clinical setting. This translational approach has been promoted to fill the existing knowledge gaps through standardization of data collection (http://www.cardioncology.it/registro_it.html). The overall purpose is to increase awareness on this emerging topic as an aid to improve patient care, in terms of quality of life and life expectancy. AIFA has also established an observational register of oncologic drugs to be intensively monitored, with the aim of promoting the appropriateness of use and guaranty access to innovative and highly expensive drugs (http://antineoplastici.agenziafarmaco.it).

Conclusions and perspectives

Novel targeted chemotherapeutics cause a variety of cardiovascular complications, which are mostly reversible as compared to those associated with traditional anticancer drugs. The question arises whether or not we are dealing with a class effect (i.e., shared by all agents of a given pharmacological class). Considering cardiotoxicity as a class effect seems speculative and each drug should be evaluated on a case-by-case basis. Notably, the benefit–risk balance between the therapeutic gain (in terms of life expectancy) and the risk of cardiotoxicity should be evaluated depending on the clinical scenario: the risk of late-

onset cardiotoxicity is not so relevant in the setting of terminal cancer, whereas early detection of cardiotoxicity remains a significant concern in long-term survivors.

While most of the uncertainties surrounding cardiotoxicity of older chemotherapeutics have now been elucidated, efforts are now needed to gain insight into cardiotoxicity associated with targeted therapies. Trastuzumab has paved the way to characterize type II versus type I cardiac dysfunction. Peculiarity and unpredictability of cardiotoxicity associated with TKIs can be tentatively classified as type III (mixed) cardiac dysfunction. In this context, the multidisciplinary area of cardio-oncology is emerging among health care professionals to ensure optimal cardiovascular management of cancer patients. Oncologists and cardiologists should combine their efforts with primary care physicians and pharmacologists and educate patients with cancer with the goal of improving long-term clinical outcomes.

All these subjects should be actively involved in proactive pharmacovigilance, including drug registries, to increase consistency and develop consensus recommendations to tailor the optimal pharmacological approach. Specifically, there is an urgent need to define clinical endpoints of cardiotoxicity and to harmonize cardiac monitoring. This would allow timely recognition of subclinical damage and proper assessment of the magnitude in the population. In this context, an independent Adjuvant Cardiac Review and Evaluation Committee prospectively established objective criteria to define events of symptomatic CHF and allow data combination of different trials [80]. Risk stratification based on host- and drug-related risk factors will allow a case-by-case approach to treat each patient.

Onco-pharmacovigilance can be a pivotal indicator of risk of cardiotoxicity in clinical practice, where patients' characteristics clearly differ from those in clinical trials (e.g., presence of co-morbidities, risk factors, borderline cardiac parameters). Long-term monitoring is needed as several novel targeted drugs (e.g., vascular-disrupting agents) are entering the pipeline [30].

In conclusion, cardiotoxicity associated with targeted therapy represents a multifaceted and multidisciplinary issue requiring actual definition and quantification. Prevention, detection, timely reporting, and treatment appear currently inaccurate and should be promoted to mitigate cardiac dysfunction associated with targeted therapy. In this scenario, the clinical pharmacologist can play an active role by providing balanced information on the risk/benefit profile of drugs for rational use of medicines. We encourage spontaneous reporting systems and registries as monitoring tools for appropriate drug use and to support optimal risk management plans, embracing risk identification, minimization and communication.

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Conflict of interest None.

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