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Invited review article

The concomitant management of cancer therapy and cardiac therapy☆

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ABSTRACT

Antitumor drugs have long been known to introduce a measurable risk of cardiovascular events. Cardio-Oncology is the discipline that builds on collaboration between cardiologists and oncologists and aims at screening, preventing or minimizing such a risk. Overt concern about "possible" cardiovascular toxicity might expose cancer patients to the risk of tumor undertreatment and poor oncologic outcome. Careful analysis of risk:benefit balance is therefore central to the management of patients exposed to potentially cardiotoxic drugs. Concomitant or sequential management of cardiac and cancer therapies should also be tailored to the following strengths and weaknesses: i) molecular mechanisms and clinical correlates of cardiotoxicity have been characterized to some extent for anthracyclines but not for other chemotherapeutics or new generation "targeted" drugs, ii) anthracyclines and targeted drugs cause different mechanisms of cardiotoxicity (type I versus type II), and this classification should guide strategies of primary or secondary prevention, iii) with anthracyclines and nonanthracycline chemotherapeutics, cardiovascular events may occur on treatment as well as years or decades after completing chemotherapy, iv) some patients may be predisposed to a higher risk of cardiac events but there is a lack of prospective studies that characterized optimal genetic tests and pharmacologic measures to minimize excess risk, v) clinical toxicity may be preceded by asymptomatic systolic and/or diastolic dysfunction that necessitates innovative mechanism-based pharmacologic treatment, and vi) patient-tailored pharmacologic correction of comorbidities is important for both primary and secondary prevention. Active collaboration of physicians with laboratory scientists is much needed for improving management of cardiovascular sequelae of antitumor therapy. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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Contents

Abbreviations: AUC, area under the curve of plasma concentration vs time; ACEI, angiotensin converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker(s); BNP, B-type natriuretic peptide; CHF, congestive heart failure; C_{max}, peak plasma concentration; EGFR, epidermal growth factor receptor; $I_{Na,Late}$, late inward sodium current; KI, kinase inhibitor(s); LVEF, left ventricle ejection fraction; MI, myocardial infarction; NO, nitric oxide; Nt-proBNP, inactive aminoterminal fragment of B-type natriuretic peptide prohormone; PDGF(r), platelet derived growth factor (receptor); ROS, reactive oxygen species; VEGF(r), vascular endothelial growth factor (receptor).

☆ This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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1. Introduction

Antitumor therapies may expose patients to cardiovascular discomfort such as transient blood pressure instability, supraventricular arrhythmias or sporadic benign ventricular arrhythmias. In the vast majority of cases such disorders occur acutely ("on-treatment"), revert spontaneously or respond to cardiovascular therapy, and do not form an indication to interrupting therapy. In other cases, however, cardiac sequelae of antitumor therapies are life-threatening. Cumulative doses of anthracyclines, mitomycin, or mitoxantrone, induce dilated cardiomyopathy and congestive heart failure (CHF) [1,2]. With the prototypic anthracycline, doxorubicin, 5% risk of CHF occurs at a cumulative dose of 400–450 mg/m^2 [3].

Our perception of the clinical manifestations of cardiotoxicity has nonetheless changed over the last years. Both retrospective and longitudinal prospective studies show that cumulative anthracycline doses lower than e.g., 400 mg of doxorubicin/m^2, cause fewer on-treatment events; nevertheless, CHF may develop five or more years after completing chemotherapy. This is seen in survivors of both childhood-adolescent and adult cancer, and suggests that there is no safe dose of anthracycline [8]. Moreover, some cancer survivors were found to develop dilated cardiomyopathy and CHF while others developed restrictive cardiomyopathy with less compromised left ventricle ejection fraction (LVEF), or developed ischemic disease and myocardial infarction (MI) [4,5]. Irradiation of cardiac area (e.g., in patients with mediastinal lymphoma) contributes to causing cardiotoxicity and in some patients, it seems to influence prevalence of ischemic disease over CHF [5]. Nonanthracycline chemotherapeutics (antimetabolites, alkylators, tubulin-active vinca alkaloids) have long been known to induce coronary endothelial dysfunction and myocardial ischemia that occurs within hours or days from treatment [2,6]; however, more recent data demonstrate that also these drugs introduce a lifetime risk of cardiovascular events [4–6]. The importance of age of first treatment has been reappraised. Children-adolescents and the elderly have traditionally been considered to be more vulnerable by anthracyclines but in defined clinical settings (breast cancer, Hodgkin lymphoma) the risk of late onset cardiac disease did not always depend on age of first treatment [5,7].

Cardiovascular events occur also with "targeted" drugs that were hoped to hit tumor cells but not the cardiovascular system and other healthy tissues. Many such drugs were in fact designed for binding to receptors or inhibiting kinases which later were identified also in healthy tissues. An antibody targeted at the epidermal growth factor receptor 2 (EGFR2), trastuzumab, precipitates CHF in breast cancer patients who receive concomitant anthracyclines, and causes moderate to severe contractile dysfunction in patients with a prior exposure to anthracyclines [1,8]. An antibody targeted at the Vascular Endothelial Growth Factor (VEGF), bevacizumab, may cause hypertension, myocardial contractile dysfunction or ischemia, peripheral vascular occlusive events [9]. Cardiovascular liability issues have been raised for sunitinib and sorafenib, small molecule inhibitors of the kinase domain of VEGF receptor (VEGFr), and for imatinib and nilotinib, small molecule inhibitors of Bcr-Abl and c-Kit of leukemic or gastrointestinal sarcoma cells [10].

The list of antitumor drugs that cause, or are suspected to cause cardiovascular events, seems to be expanding inexorably. A detailed analysis of the library of drugs possibly involved in cancer treatment-related cardiovascular events is not in the scope of this review. We would rather address some controversial issues that need to be put in context before one examined which patients would benefit most from cardiovascular prevention or treatment.

2. Mechanistic foundations for cardiovascular therapy in cancer patients: strengths and weaknesses

Mechanism-based approaches to preventing or treating cardiovascular sequelae of antitumor therapies should build on a comprehensive appraisal of how antitumor drugs cause cardiovascular toxicity. As disappointing it may sound, one such understanding is still lacking. A mechanistic insight is available for relatively few drugs.

Anthracyclines have been around for more than 40 years and many theories of anthracycline-induced cardiotoxicity have been advanced. Anthracyclines, which kill tumor cells by DNA intercalation and topoisomerase IIα inhibition, seem to induce cardiotoxicity by a constellation of mechanisms that go from oxidative stress to mitochondriopathy, changes in the expression and architectural coupling of respiratory chain components, and alterations of iron and calcium homeostasis [1,8]. Cause-and-effect relations or reciprocal interactions between one mechanism and the others are nonetheless uncertain. More recently, a unifying mechanism of cardiotoxicity was proposed: it envisioned formation of anthracyline-DNA-topoisomerase 2β complexes that caused DNA double-strands breaks and transcriptional changes associated with impaired mitochondrial biogenesis and function [11]. With that said, not all of the patients exposed to a given anthracycline dose will develop cardiomyopathy and CHF [6]. Genetic predisposition may come into a play and determine the individual risk and clinical pattern of development of cardiotoxicity. For example, two electron reduction of a carbonyl group in the side chain of anthracyclines generates secondary alcohol metabolites that are more polar than their parent drugs, exhibits a reduced elimination from cardiac tissue, and accumulates to form a long-lived cardiac reservoir of anthracycline [2,8,12–17]. It follows that regardless of the soundness of one molecular mechanism of toxicity or another, the risk of cardiotoxicity may ultimately depend on individual changes in the net levels of formation of secondary alcohol metabolites.

One should also comment on some disconnections between molecular pathways and clinical manifestations of anthracycline cardiotoxicity. The aforesaid mechanisms, primarily centered on mitochondrial dysfunction and formation of reactive oxygen species (ROS), fit quite well in a canonical phenotype of dilated cardiomyopathy and CHF. As it was said earlier, however, certain patients (childhood cancer survivors) developed subclinical dilated cardiomyopathy that eventually progressed to restrictive cardiomyopathy with preserved or less compromised LVEF [18]. Anthracycline-induced gene expression changes that caused cardiac remodeling and collagen deposition should therefore be taken in a due consideration [19]. On balance, it seems that even for 40-years old drugs, like anthracyclines, the mechanisms and clinical correlates of cardiotoxicity remain too vague or unexplored to form a solid basis for choosing one defined strategy of prevention or treatment.

For newer drugs our knowledge is even less adequate. In the case of small-molecule kinase inhibitors (KI), mechanisms of cardiovascular toxicity not only are multifactorial but also involve a blending of "on-target" and "off-target effects". Clinical reports of sunitinib-induced cardiotoxicity showed that LVEF decreased because of hemodynamic challenge from hypertension [20]. This did not come as surprise. Sunitinib was developed to inhibit angiogenesis by targeting the tyrosine kinase domain of VEGFr. By silencing VEGF–VEGFr signaling pathway, sunitinib reduces capillary density and mitigates formation and vasodilating effects of nitric oxide (NO), thereby causing hypertension that stresses the heart. Sunitinib also inhibits the kinase domain of platelet derived growth factor receptor (PDGFr) and prevents cardiomyocytes from responding to stress by secreting pro-angiogenic factors [21]. This is on-target toxicity that develops through an anticipated poisoning of VEGFr and PDGFr. However, sunitinib cardiotoxicity might occur also through direct effects on cardiomyocytes that remain poorly characterized. Again, but for different reasons, this is anything but surprise. VEGFr and PDGFr are two limited examples of the very many potential targets of sunitinib. This drug inhibits also AMP-activated protein kinase but at therapeutic plasma levels, it concomitantly inhibits some other 90 kinases. Inhibition of which kinase or combination of kinases caused cardiotoxicity from sunitinib would be very difficult to identify [22].

Off-target effects from "targeted" drugs may occur also in cells other than adult cardiomyocytes. In addition to inhibiting Bcr-Abl and c-Kit, the antileukemic drug, imatinib, can block proliferation of c-Kit negative side-population cardiac stem cells via binding to breast cancer resistance protein [23]. In principle, this effect might prevent cardiac repopulation and recovery of cardiac function if other noxae had irreversibly damaged a critical number of adult cardiomyocytes. And finally, in vitro models showed that myocyte damage from a broad panel of KI correlated with lack of target specificity [24]. In light of the emergence of unpredictable off-target effects, one cannot escape the conclusion that mechanistic foundations for preventing or treating "direct" cardiotoxicity from "targeted" drugs are still lacking. This having been recognized, possible disconnections between preclinical findings and clinical facts should always be taken in a due account. In the case of imatinib, recent clinical surveys suggest that concerns about cardiotoxicity may have been overemphasized. Imatinib cures patients of chronic myeloid leukemia without causing cardiac events of major importance [25,26].

By having illustrated the many factors that limit our understanding of cardiotoxicity at a molecular level, we would now emphasize that preclinical and clinical phenotypes of cardiac dysfunction from anthracyclines or newer drugs are different enough to suggest a classification that guides clinical management of cancer patients. This classification is inspired by different effects induced by trastuzumab administered alone, in combination with anthracyclines, or after anthracyclines.

In the adult human heart trastuzumab alone causes a contractile dysfunction that develops dose-independently, shows reversibility upon medication or trastuzumab withdrawal, may not relapse upon rechallenge, and only occasionally induces ultrastructural damage at endomyocardial biopsies [27]. The characteristics of trastuzumab cardiotoxicity are quite opposite to those of anthracyclines, whose cardiotoxicity develops dose-dependently, causes changes of endomyocardial biopsies, precipitates upon rechallenge, and may not always respond to cardiovascular drugs [1]. These notions have formed the basis to classify anthracyclines as type I agents, and trastuzumab as type II agent [28]. This having been said, how does trastuzumab aggravate cardiotoxicity of concomitant anthracycline? The current thinking is that by blocking EGFR2 and autophosphorylation of its kinase domain, trastuzumab silences downstream signalling factors (Grb2, ras, Raf, MAPK, P13K, Akt) that modulate gene expression and cell growth, glucose uptake, and sarcomeric protein turnover [29]. All such survival-oriented signals may be redundant in the healthy unchallenged heart but prove to be life-saving if cardiomyocytes were challenged by anthracyclines. In other words, blocking EGFR2 with trastuzumab aggravates anthracycline cardiotoxicity by diminishing survival and repairs mechanisms of the heart. It was in keeping with these concepts that administering trastuzumab weeks or months after anthracyclines nearly abated the risk of serious cardiac events and became routine practice in the settings of adjuvant chemotherapy of early breast cancer [30]. Here it is worth of noting that trastuzumab lacked cardiotoxicity in preclinical murine models; in fact, trastuzumab does not recognize the ectodomain of murine EGFR2 [31]. Trastuzumab binds to primate EGFR2 but only few primates were used in preclinical tests and none of them was treated with anthracyclines. Again, these facts denote that preclinical studies do not always help to anticipate clinical cardiotoxicity of one agent or another [2,32].

Other "targeted" drugs may be similar to trastuzumab in many respects. In preclinical settings, sorafenib per se caused little or no damage to the heart but remarkably aggravated mortality of experimental-induced myocardial infarction, as if sorafenib caused trastuzumab-like silencing of factors that helped cardiomyocytes to withstand stressor conditions [33]. In clinical settings, bevacizumab aggravated cardiotoxicity of concomitant anthracyclines regardless of blood pressure changes, which was similar to what trastuzumab did in patients receiving concomitant anthracycline [34]. And finally, retrospective analyses show that cardiovascular events from sunitinib denote significant reversibility, such that many patients were able to resume sunitinib dosing following spontaneous of pharmacological resolution of events [35]. All such findings suggest that the classification of type II agent might be extended to including sunitinib and possibly, other targeted drugs (Table 1).

Table 1
Cardiovascular events from type I or type II antitumoral agents.

Preclinical and clinical findings	Type I agents (anthracycline)	Type II agents (trastuzumab, sunitinib; other targeted agents?)
Mechanism	Multifactorial damage to cardiomyocytes	Silencing of survival factors, impaired cardiomyocyte survival to hemodynamic challenges or concomitant anthracycline
Dose-dependence	Cumulative	Lack of evidence for dose-dependence
Clinical phenotype	CHF with normal or decreased LVEF, Ischemic disease and myocardial infarction	CHF with decreased LVEF (trastuzumab); hypertension, decreased LVEF, thrombosis and thromboembolism (sunitinib and other angiogenesis inhibitors)
Ultrastructure	Apoptosis or necrosis at endomyocardial biopsies	With limited exceptions, no apparent ultrastructural abnormalities
Clinical course	May stabilize, but subclinical damage persists and progresses to clinical symptoms over months or years	High likelihood of complete or near-to-complete recovery upon withdrawal and/or medication
Effect of rechallenge	High probability of cardiac events	Increasing evidence for the safety of rechallenge

Adapted, with modifications, from refs. [2,27]
LVEF, left ventricular ejection fraction.

3. Balancing oncologic efficacy with cardiovascular outcome: primary prevention

Preventing a disease is better than treating it. This dictum holds true also in Cardio-Oncology. As shown in Fig. 1, the risk of cardiovascular events and the need for treatment gradually increase if cancer patients are denied primary and/or secondary prevention. Some strategies of primary prevention are specific to patients candidate for anthracycline-based treatments; others are less specific and can be applied to any patient undergoing chemotherapy.

3.1. Primary prevention of cardiotoxicity from anthracyclines

Anthracycline cardiotoxicity can be reduced by replacing bolus administration with slow infusions over 5 to 96 h. This strategy builds on well defined pharmacokinetic determinants of anthracycline activity and cardiotoxicity. Whereas activity correlates with total plasma exposure to anthracyclines (as exemplified by the area under the curve of plasma anthracycline concentration vs time, AUC), the risk of CHF correlates with peak plasma level of anthracyclines (C_{max}) and their consequent diffusion and accumulation in the heart. Replacing bolus administration with slow infusions does not significantly affect anthracycline AUC but diminishes anthracycline C_{max} and anthracycline accumulation in the heart [1]. Cardiac safety of slow anthracyclines infusions has been documented in numerous studies, even when anthracyclines were administered in cumulative doses known to induce CHF [1].

Anthracycline cardiotoxicity can be reduced also by replacing conventional anthracyclines with liposomal formulations. These latter are too big to cross the gap junctions of endothelial linings in the heart and many other healthy tissues; however, liposomal formulations are small enough to cross the irregular and leaky microvasculature that characterizes many solid tumors [1]. One liposomal doxorubicin (Caelyx® in Europe, Doxil® in US) has polyethylene glycol embedded in the lipid layer; other formulations of doxorubicin (Myocet®) or daunorubicin (Daunoxome®) adopt uncoated liposomes. Following extravasation in tumors, liposomal formulations accumulate by virtue of the insufficient lymphatic drainage and increased interstitial pressure that characterize many tumors. And in addition, tumor microenvironment destabilizes the liposomal vesicle through a variety of mechanisms that go from low pH to the release of lipases from dying tumor cells or the release of enzymes and oxidizing agents by tumor-infiltrating inflammatory cells. In the case of uncoated formulations, also the phagocytic cells residing in tumors could metabolize liposomes and release active free anthracycline [1]. Liposomal formulations therefore deliver substantial amounts of anthracycline in tumors but much less so in the heart, offering advantages quite similar to slow infusions. Regardless of obvious pharmacokinetic and toxicokinetic differences between uncoated and pegylated formulations, all liposomal anthracyclines proved to be active and reasonably cardiac tolerable in a number of clinical trials [36,37]. Efficacy and safety were also seen when uncoated or pegylated liposomal doxorubicin was used in combination with trastuzumab, i.e., under conditions when conventional doxorubicin and trastuzumab had proved to synergize and to cause unacceptable cardiotoxicity [38,39].

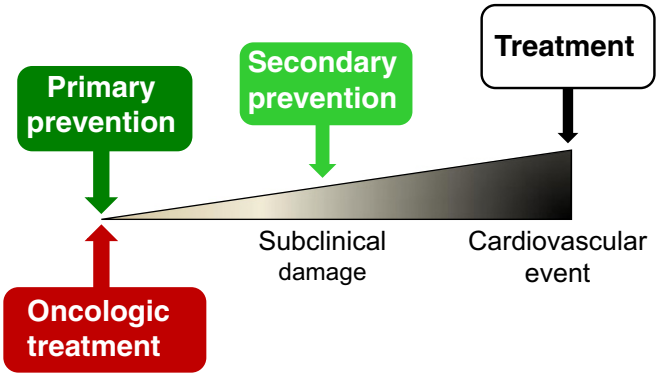

Fig. 1. Prevention or treatment of cardiovascular events in cancer patients. The risk of cardiovascular events and the need for treatment increase gradually as cancer patients were denied primary and/or secondary prevention.

Another possible strategy for preventing cardiotoxicity could be the replacing of a given anthracycline with an equiactive but less cardiotoxic cogener. The number of "less cardiotoxic" analogs keeps growing but after all, unambiguous clinical validation of a "less cardiotoxic" analog is still lacking [1]. 4′-Epidoxorubicin (epirubicin) has long been said to cause less cardiotoxicity than doxorubicin. Interestingly, however, epirubicin also shows improved body clearance and therefore causes less antitumor activity when administered equimolar to doxorubicin. If epirubicin is administered in higher doses to compensate for increased elimination and to attain the same activity as that of doxorubicin, the risk of cardiotoxicity increases, particularly in the elderly or in patients with defined risk factors [40]. Amrubicin and the novel anthracenedione, pixantrone, are noticeably less cardiotoxic than doxorubicin but unfortunately they are approved for use in very limited conditions [15–17]. Other strategies for reducing anthracycline cardiotoxicity were based on the coadministration of drugs or natural compound that improved the antioxidant defenses of cardiomyocytes against oxidative stress. Regrettably, neither vitamin E nor N-acetylcysteine proved able to prevent cardiotoxicity in patients exposed to cumulative doses of doxorubicin [1]. These findings might cast doubts on cause-and-effect relations between oxidative stress and cardiotoxicity, unless one assumed that antioxidant dosages were not high enough for one compound or the other to permeate cardiac sanctuaries exposed to oxidative damage.

Historically, the most popular strategy for preventing anthracycline cardiotoxicity was based on the coadministration of dexrazoxane. This latter is a bis-ketopiperazine which enters cardiomyocytes, undergoes stepwise hydrolysis of its piperazine rings, and forms an EDTA-like diacid-diamide that chelates iron [1]. Iron chelation and mitigation of iron-catalyzed free radical reactions were therefore considered to be culprits of the cardiac protective efficacy of dexrazoxane [1,41]. In subsequent years, however, dexrazoxane was shown to inhibit topoisomerase IIα (in proliferating cells) and topoisomerase IIβ (in cardiomyocytes and other quiescent cells) [42]. In cardiomyocytes, dexrazoxane inhibition of topoisomerase IIβ prevented doxorubicin-induced DNA double strand breaks and cell death. Regardless of its multiple modes of action, dexrazoxane was able to prevent anthracycline-related cardiotoxicity in many clinical studies of both childhood and adult cancer patients, often allowing for the administration of anthracycline doses above the threshold associated with risk of CHF [1]. Dexrazoxane was the only drug that granted approval from US Food and Drug Administration for use as cardiac protectant in patients exposed to anthracyclines.

Each of the aforesaid strategies of primary prevention should be scrutinized for risk:benefit ratio. Slow infusions limit patients' compliance, and doctors perceive them as too laborious and demanding to be done on a routine basis. Perhaps more importantly, protective efficacy of slow infusions in children with acute lymphoblastic leukemia has been questioned [43]. Liposomal formulations cause more mucositis, hand–foot syndrome, and present obvious problems of cost sustainability [1]. Moreover, liposomal anthracyclines are approved for use in only limited settings (metastatic breast cancer for uncoated liposomal doxorubicin; metastatic breast cancer, advanced/refractory ovarian cancer or multiple myeloma, AIDS related Kaposi's sarcoma, for pegylated liposomal doxorubicin; AIDS related sarcoma for liposomal daunorubicin).

As to dexrazoxane, its clinical usage was limited by just one report of its possible interference with anthracycline activity in metastatic breast cancer [44]. In addition to inhibiting topoisomerases, dexrazoxane is

also known for its weak alkylating activity [41]. An interference of dexrazoxane with anthracycline activity might therefore fit in a scenario in which a moderate–weak antitumor agent (dexrazoxane) competed with a stronger agent (anthracycline) for critical DNA or topoisomerase sites. This has never been demonstrated [45]. In contrast, an overwhelming body of clinical studies demonstrates that dexrazoxane did not diminish anthracycline activity [8,45]. The American Society of Clinical Oncology, Chemotherapy, and Radiotherapy Expert Panel maintained caution and recommended using dexrazoxane only in very limited conditions (e.g., patients who have received more than 300 mg/m^2 for metastatic breast cancer and who may benefit from continued doxorubicin treatment) [46]. We suggest that the time has come for revisiting this cautionary position. Another controversial issue about dexrazoxane pertains to an increased risk of second malignancies. This was observed in survivors of Hodgkin lymphoma who had received doxorubicin in combination with etoposide. By having considered that both doxorubicin and etoposide and dexrazoxane inhibited topoisomerase IIα, albeit by different mechanisms and with different efficacies, it was postulated that combining the three drugs could exceed a threshold above which topoisomerase inhibitors caused genetic instability in normal tissues [47]. This report led the European Medicine Agency to conclude that dexrazoxane should not be used in children due to the risk of second malignancies. Two studies of survivors of childhood acute lymphoblastic leukemia reached opposite conclusions and did not detect an increased risk of second malignancies from dexrazoxane [48,49]. We believe that risk: benefit analysis supports a wider clinical usage of dexrazoxane with the possible exception of conditions in which patients received etoposide or etoposide-anthracycline combinations.

Slow infusions, liposomal formulations, and dexrazoxane, are prototypic examples of pharmacologic strategies for primary prevention of anthracycline cardiotoxicity. The advancement of knowledge and identification of genetic variants that put patients at a higher risk of anthracycline-related cardiotoxicity suggest that the time might be mature for developing other strategies. The key role of long-lived secondary alcohol metabolites, and the reported observation that patients with type 3 carbonyl reductase V244M homozygous G genotype formed higher levels of metabolites and developed CHF after exposure to low cumulative anthracycline doses, should form a rationale to screen for enzymatic variants before a patient was treated anthracyclines [50]. By a similar approach but for different reasons, measurements of topoisomerase 2β levels in circulating blood leukocytes might be used to stratify patients for cardiotoxicity risk [51]. Recommendations about avoiding anthracyclines or reducing anthracycline dosages in patients with CBR3 polymorphisms or high topoisomerase 2β levels should nonetheless be validated by large prospective studies. Similar limitations apply to the screening of other genetic factors that were shown to predispose to anthracycline cardiotoxicity (reduced expression of pro-survival coactivators like T-cell leukemia/lymphoma protein 1A or of multidrug resistance protein 1 [52], mutations associated with familial cardiomyopathy [53,54]).

General concepts of primary prevention of anthracycline cardiotoxicity are summarized in Table 2.

3.2. Primary prevention of cardiotoxicity from any agent

For any chemotherapeutic agent with a known or suspected potential for inducing cardiotoxicity, primary prevention is achieved by measures that rest on common sense. Pre-existing comorbidities (hypertension, systolic dysfunction, arrhythmias, metabolic disorders) or unfavorable lifestyle choices (smoking, overweight, reduced physical activity) have long been known to increase the risk of cardiotoxicity in patients scheduled to receive anthracyclines [1]. This notion can safely be extended to cardiotoxicity from any other agent and calls for vigorous pharmacological correction of pre-existing comorbidities before chemotherapy was started [23]. And importantly, an appraisal of pre-existing comorbidities should not be exploited to replace one cardiotoxic agent with another agent that is less cardiotoxic but also shows lower oncologic efficacy. In the settings of anthracyclines, one might consider using liposomal formulations. In some European countries, national health systems actually encourage off label usage of liposomal anthracyclines in high risk patients. For “targeted” drugs with type II cardiotoxicity, evidence of reversibility and of safety at rechallenge strongly advise to not abandon the opportunity of optimal treatment, provided that pre-existing risk factors were adequately controlled by cardiovascular or metabolic drugs.

Some reports suggest that cardiovascular drugs should be administered also to patients without risk factors. Significant cardiac protection, measured as preservation or limited decrease of LVEF, was seen in studies of carvedilol (α_1 and β_{1-2} adrenoceptor blocker) [55], nebivolol (β_1 blocker) [56] or a combination of carvedilol with the angiotensin converting enzyme inhibitor (ACEI), enalapril [57]. Less protection was seen with metoprolol (β_1 blocker) or enalapril alone [58]. The

Table 2
Primary prevention of anthracycline cardiotoxicity.

Measure	Mechanism of protection	Anticipated clinical benefit	Disadvantages/limitations
Slow infusions	Normal anthracycline AUC but lower C_{max}	Preserved anthracycline activity with reduced risk of cardiotoxicity	Poor patients' compliance, laborious and demanding in clinical practice, lack of cardiac protection in children with acute lymphoblastic leukemia.
Liposomal formulations	Limited diffusion through the gap junctions of coronary microvasculature	Improved cardiac tolerability; safe administration with concomitant trastuzumab	Mucositis, hand–foot syndrome, high costs, limited approved indications.
Dexrazoxane	Iron chelation and mitigation of ROS formation/reactivity, inhibition of topoisomerase IIβ-mediated DNA double strand breaks	Prevention of cardiotoxicity in both childhood and adult cancer	Interference with anthracycline activity and increased incidence of second malignancies (unconfirmed and/or dispelled)
Antioxidants	Mitigation of oxidative stress	Reduced incidence of CHF?	Unproven efficacy (limited cardiac penetration of antioxidants?)
Less cardiotoxic analogs	Reduced activation and toxicity mechanisms	Reduced incidence of CHF?	Under scrutiny; reduced cardiotoxicity of amrubicin and pixantrone in limited approved settings
Screening for CB3 polymorphisms, topoisomerase IIβ levels, deficiencies in TCL1A or MDR1 protein genes, familial cardiomyopathy mutations	Identification of at-risk patients	May guide dose adjustments?	Investigational

AUC, area under the curve of plasma concentration versus time; C_{max}, peak plasma concentration; ROS, reactive oxygen species; CBR3, type 3 carbonyl reductase; TCL1A, T-cell lymphoma/leukemia protein 1A; MDR1, multidrug resistance protein 1.
See also text for explanations.

rationale for using carvedilol or nebivolol was influenced by some pharmacodynamic reasonings. In addition to blocking adrenergic receptors, cardvedilol diminished ROS formation in isolated cardiomyocytes exposed to doxorubicin [59]. Nebivolol induced endothelial nitric oxide (NO) synthase expression, thereby favoring NO-mediated vasodilation [60]; nebivolol also prevented NO synthase uncoupling, inappropriate generation of peroxynitrite, nitroxidative stress [61]. The available evidence nonetheless suggests that beneficial effects from one β blocker or another eventually depends on its affinity and selectivity for β_1 receptors [$K_i(\beta_2)/K_i(\beta_1)$] and on consequent effects such as reductions in rate-pressure products and mitigation of myocardial remodeling. This information was obtained in patients exposed to anthracyclines but we believe that there is no conceptual obstacle to anticipating beneficial effects also in patients exposed to targeted agents that cause e.g., vasoconstriction and hypertension.

An observational clinical cohort study of breast cancer patients treated with anthracyclines suggests that also statins could reduce the risk of CHF [62]. This finding is consistent with animal studies and with the notion that simvastatin protected cardiomyocytes via activation of nitric oxide synthase and mitochondrial ATP sensitive potassium channels [63]. Interestingly, however, statin effects were most evident in patients who received other cardiovascular drugs for preexisting risk factors. It remains to be established whether statin effects were coincidental or reflected one or more independent pharmacodynamic effects.

Primary prevention of thrombotic or thromboembolic events from targeted agents is even less firmly established. There is no approved guideline that recommends prophylactic commencement of antiplatelet agents and/or anticoagulants nor preferential usage of an agent over another. Oncologic treatment should be preceded by careful analysis of patient's records of previous coagulation disorders and by laboratory assessment of thrombophilic risk factors. Patient's surveillance during the course of treatment, and serial monitoring of laboratory indices like platelet count/reactivity and prothrombin time, are obviously advised and should guide antiplatelet and/or anticoagulant interventions at the very early signs of vascular damage.

Again, each of the aforesaid strategies of primary prevention needs to be scrutinized for risk:benefit balance. Many doctors believe that in patients without risk factors, discomforts from chemotherapy (fatigue, nausea, vomiting) should not be aggravated by class-related effects of cardiovascular drugs (bradycardia, hypotension, fluid retention, cough). We believe that judicious perception of the risk of cardiotoxicity should eliminate this conceptual barrier to primary cardiovascular prevention. On the other hand, many commonly used medications for cardiovascular disease may alter metabolism and/or transport of anticancer drugs [23]. A risk of harmful pharmacokinetic interactions cannot be ruled out. One can only recommend that in patients without risk factors, cardiovascular drugs were used at “prophylactic” rather than “therapeutic” dosages. Prospective randomized trials are needed to define the efficacy and dose relations of primary prevention with cardiovascular drugs as well as its impact on short and long term efficacy of oncologic treatment. With particular regard to angiogenesis inhibitors we would comment on the possible positive correlation between the oncologic efficacy of these drugs and their ability to induce hypertension through vasoconstriction and reduced capillary density [9,64]. Inasmuch as tumor growth, invasion and metastatization, depend on blood supply to cancer cells, one might wonder whether drugs that prevented hypertension through vasodilation could also restore blood supply to tumor cells and diminish oncologic efficacy to some extent. In the absence of studies that explored this issue in depth, common sense and judicious assessment of patient-specific risk:benefit balance must prevail. Drugs that lowered blood pressure by controlling cardiac output (β blockers) should be preferred over drugs that caused vasodilation (α blockers, ACEI, angiotensin II receptor blockers (ARB), peripheral dihydropyridine-type Ca^{2+} channel blockers).

General concepts of primary prevention of cardiovascular events from any agent are summarized in Table 3.

4. Secondary prevention

4.1. Methodological limitations and available evidence

Secondary prevention requires that patients be monitored during and after therapy and be managed when toxicity signals appear. But how can toxicity be defined? Problems in defining cardiotoxicity at a molecular level translate into uncertainties in clinical settings. And what action or actions should be taken to protect patients if a laboratory or clinical finding met a definition of cardiotoxicity?

According to some recommendations, cardiotoxicity should be adjudicated as soon as a patient developed symptoms of CHF or asymptomatic decreases of LVEF [65]. This is a careful and conservative definition that nonetheless suffers from potential downside. In some patients LVEF returned to baseline if chemotherapy was stopped but in other patients LVEF returned to baseline also when chemotherapy was continued [66]. In cancer patients LVEF may decrease by factors that do not always reflect drug-related cardiotoxicity (e.g., hydration status, anemia, infections, transient neurohumoral changes). Binding decisions to occasional decreases of LVEF would expose patients at risk for treatment discontinuation and poor oncologic outcome. Decisions about interrupting life-saving antitumor therapies should better rest with serial measurements that detected gradual but inexorable deterioration of LVEF. This can only be done in centers that developed collaborations between oncologists and cardiologists; however, there is a lack of approved guidelines that precisely defined how often should e.g., LVEF be measured during and after treatment. Cardiotoxicity has recently been defined also by means of circulating levels of cardiac biomarkers. In blood samples collected after ending

Table 3
Primary prevention of cardiovascular events from any agent.

Measure	Mechanism of protection	Anticipated clinical benefit	Disadvantages/limitations
Pharmacologic correction of comorbidities in high risk patients	Mitigation of cardiovascular, metabolic, and lifestyle risk factors	Reduced incidence of on-treatment cardiac events	None.
Coadministration of ACEI, ARB, β-blockers, in low risk patients	Reductions of rate-pressure products and mitigation of cardiac distress	Improved cardiac tolerability of antitumor agents	Possible pharmacokinetic interactions with antitumor drugs (need for dose finding studies); possible pharmacodynamic interference of ACEI, ARB, or peripheral Ca^{2+} antagonists, with angiogenesis inhibitors?
Statins	Activation of nitric oxide synthase and mitochondrial ATP sensitive potassium channels (preclinical evidence only)	Reduced incidence of CHF	None, but the role of potential confounders (concomitant cardiovascular drugs) needs to be elucidated
Antiplatelet drugs, anticoagulants	Reduction of platelet activation and inappropriate blood coagulation	Reduced incidence of thrombosis and thromboembolism	Lack of guidelines

ACEI, angiotensin converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker(s); CHF, congestive heart failure. See also text for explanations.

Table 4
Secondary prevention.

Measure	Mechanism of protection	Clinical benefit	Disadvantages/limitations
Treatment withdrawal as soon as LVEF decreases	Removal of the cardiotoxic agent or agents	LVEF normalizes	Limited predictive value of LVEF decreases (LVEF may normalize even if treatment was not stopped), risk of tumor undertreatment
Monitoring of post-infusional levels of troponin I in patients with normal LVEF	Detection of cardiomyocyte necrosis and identification of patients at risk for loss of contractile function	May guide early commencement of ACEI to prevent LVEF decreases and CHF	Information limited to patients with prior chemotherapies or exposed to high dose chemotherapy protocols
Monitoring of contractile function indices after ending chemotherapy	Unraveling asymptomatic subclinical cardiac dysfunction	May guide therapy with ACEI to prevent further deterioration of left ventricle function	Cardiotoxicity progresses after transient improvements
Surveillance and correction of chemotherapy-related chronic health conditions	Preventing the overlap of newly developed comorbidities with subclinical cardiotoxicity	Reduced risk of late cardiovascular sequelae	None

ACEI, angiotensin converting enzyme inhibitor(s); CHF, congestive heart failure
See also text for explanations.

chemotherapy infusions, troponin I elevations denote necrosis of a definite number of cardiomyocytes and may identify patients at risk for loss of contractile function [67].

Some studies examined the efficacy of β-blockers or ACEI in patients who developed cardiotoxicity as defined by means of decreases of LVEF or elevations of troponin I. In one study, enalapril was given to patients who showed persistent elevation of troponin I at 72 h from chemotherapy infusions. In comparison with patients without enalapril, those who received enalapril showed significantly higher LVEF at 1-year follow-up; moreover, patients without enalapril showed a disturbing incidence of LVEF decreases to below 50% [67]. It is worth noting that troponin I elevations occurred primarily in patients who had received prior oncologic treatment and then underwent second or third line treatment with high dose chemotherapy. Predictive value of troponin elevations in patients undergoing first line standard dose chemotherapy remains to be established. In childhood cancer survivors, starting enalapril some 7 years after ending an anthracycline-based treatment offered measurable improvements in many indices of left ventricle structure and functions; however, the improvements did not last longer than 6 years [68]. This study suggested that late commencement of enalapril failed to stop cardiac remodeling but caused blood pressure-rate reductions that only transiently delayed it. Earlier enalapril commencement, possibly guided by troponin I elevations during the course of chemotherapy, might have been of greater efficacy in these patients.

4.2. Multiple hits and importance of surveillance

In the absence of universal imaging or biohumoral markers for the lifetime risk of cardiotoxicity, one should look at cardiotoxicity and hence, at secondary prevention, from alternative but not mutually exclusive viewpoints. Comorbidities play a key role in this setting. We mentioned that preexisting comorbidities or unfavorable lifestyle choices put patients at a higher risk to develop cardiovascular sequelae of antitumor treatment. The available evidence suggests that this picture should be viewed also the other way around: in comparison with age-matched controls, previously healthy survivors of adolescent or adult cancer develop more comorbidities or tend to reduce physical activity [69,70]. In childhood cancer survivors, 10% of 50-year-old patients carry three chronic health conditions, with ~50% and ≥20% cumulative incidence of, respectively, first and second condition. Age-matched siblings would carry only one or two conditions, with ≤20% cumulative incidence of the first condition [23]. It follows that in cancer survivors, potentially reversible subclinical cardiotoxicity (unheralded by LVEF decreases or troponin elevations) may progress toward symptomatic cardiotoxicity by overlapping with risk factors that matured after ending chemotherapy. In patients exposed to anthracycline-based regimens, comorbidities would overlap with the cardiac reservoir of secondary alcohol metabolites [2,6,8]. In patients exposed to platinum compounds, comorbidities would overlap with drug that accumulates in the intima of arteries [71]. This is the so-called "multiple-hit hypothesis" [2,6,8,70]. These concepts call for new approaches to the caring of cancer survivors. Surveillance modalities and comorbidity treatment should be tailored to the characteristics of each survivor and data show that patients' outcome improves significantly if survivors referred to cancer centers with expertise in long term surveillance [69]. Much of this information derives from patients treated with anthracyclines and nonanthracycline chemotherapeutics. Less is known about the possible incidence of chronic health conditions in survivors of cancer treated with targeted agents. The concept of type II toxicity should argue against overt concern but more data are needed to draw firm conclusions.

General concepts of secondary prevention are summarized in Table **4**.

5. New avenues

We illustrated the problems that cardio-oncologists face in assisting cancer patients and survivors at risk for cardiovascular events. We said relatively little of what can be done when patients developed severe symptoms during or after treatment. Although the mechanistic classification of antitumor drugs in type I and type II agents would intuitively call for different therapeutic approaches [23], the pharmacologic armamentarium of cardio-oncologists does not meet this requirement but rests with the same cardiovascular drugs (ACEI, ARB, β blockers, inotropic agents, Ca^{2+} channel blockers, diuretics). More should be done in the settings of prevention.

5.1. Improving primary prevention in children with cancer

Our appraisal of the lifetime risk of cardiovascular sequelae of antitumor therapies originates primarily from epidemiologic studies of childhood cancer survivors. The life expectancy of these patients is long enough to allow for subclinical cardiotoxicity to become symptomatic through the multiple hits mechanism and, in the case of anthracyclines, through the slow but inexorable accumulation of secondary alcohol metabolites in the heart. Regrettably, however, there is a lack of primary prevention studies with liposomal anthracyclines that caused limited cardiac exposure to anthracycline and proved to be more cardiac tolerable than conventional formulations in adult patients. Fifteen observational studies described the use of liposomal anthracyclines in children with cancer but most patients had been treated extensively in the past and hence, they had already been primed to risk of cardiotoxicity [72]. There is a solid rationale and compelling need for studies that evaluated liposomal anthracyclines as first line agents for pediatric cancer. These studies should include a follow-up that was long enough to decipher the impact of liposomal anthracyclines on both oncologic and cardiovascular outcomes.

5.2. Considering primary prevention in the elderly

Older cancer patients are often undertreated because of fear of toxicity. This may lead to adopt treatment regimens that lack curative effects, particularly when anthracyclines are given in lower doses or fewer cycles or are replaced by other drugs. There is a tendency to ignore that the elderly may benefit from the same cardioprotective strategies we described for younger patients. On the other hand, there is a limited but persuasive evidence that even conventional anthracyclines could be safely administered to the elderly at risk for cardiotoxicity, provided that the cumulative full dose was split in more numerous cycles compared to the standard regimen adopted in younger patients [73].

5.3. Improving secondary prevention with new markers and drugs

As for secondary prevention, we believe that more studies are needed to explore the value of natriuretic peptides that are secreted by ventricular cardiomyocytes under conditions of stress [74]. In particular, active B-type natriuretic peptide (BNP) and the inactive aminoterminal fragment of its prohormone (Nt-proBNP) may help to detect left ventricle distress in asymptomatic patients with normal LVEF [75]. We foresee developments also in the settings of imaging techniques. Echocardiographic measurements of strain and strain rates, indices of myocardial deformation, may help to detect asymptomatic abnormalities in patient at risk for delayed decreases of LVEF and symptomatic CHF [76]. The clinical utility of these biomarkers should be validated in large multiinstitutional studies.

Secondary prevention should also benefit from studies that identify diastolic dysfunction as the earliest manifestation of both on-treatment and delayed cardiotoxicity. Asymptomatic cancer survivors often present echocardiographic indices of diastolic dysfunction (impaired relaxation, stiffness) [4,71,77]. In non-oncologic settings, diastolic dysfunction may progress toward CHF with preserved LVEF and eventually, toward CHF with reduced LVEF [78]. In oncologic settings, progression of cardiotoxicity from asymptomatic diastolic dysfunction to CHF might equally well be driven by several factors. Almost all of chronic health conditions that develop in cancer survivors (hypertension, diabetes, dyslipidemia) can aggravate diastolic dysfunction [75]. Asymptomatic but persistent diastolic dysfunction progresses also toward ischemic disease; in fact, myocardial stiffness increases interstitial pressure and diminishes coronary conductance, eventually inducing conditions of limited oxygen supply to cardiomyocytes [75]. The pathophysiology of diastolic dysfunction therefore embraces the main clinical phenotypes of cardiotoxicity (CHF with normal LVEF, CHF with reduced LVEF, ischemic disease). The available evidence suggests that diastolic dysfunction could be detected a few months after ending chemotherapy [79], but the possibility that it developed earlier during the course of chemotherapy should not be ignored.

Common cardiovascular drugs are not specific enough to cure diastolic dysfunction [80]. There are hopes that diastolic dysfunction could be cured with ranolazine, a drug approved for the treatment of chronic angina. Ranolazine relieves chronic angina by inhibiting diastolic late inward sodium current ($I_{Na,Late}$). In the repolarizing ischemic heart there is delayed and/or incomplete inactivation of $I_{Na,Late}$. This causes elevation of intracellular Na^+, which exchanges with extracellular Ca^{2+} via the reverse mode Na^+–Ca^{2+} exchanger. Excess Ca^{2+} entry activates myofilaments, increases diastolic left ventricle wall stiffness, reduces coronary conductance, and therefore causes further ischemia [81]. By inhibiting $I_{Na,Late}$ ranolazine breaks a vicious cycle in which ischemia begets ischemia.

In patients with chronic angina, $I_{Na,Late}$ is activated by hypoxia, accumulation of ischemic metabolites, and overproduction of ROS [82]. A similar activation may occur in cardiomyocytes exposed to anthracyclines that consume oxygen and form ROS by continuous reduction–oxidation of their quinone moiety; moreover, anthracyclines increase cytoplasmic Ca^{2+} by mechanisms that go from an increased sarcoplasmic release of Ca^{2+} to an impaired sequestration of Ca^{2+} in mitochondria or sarcoplasmic reticulum [1,75]. Anthracycline-induced diastolic dysfunction should therefore be a good target for drugs, like ranolazine, that inhibited $I_{Na,Late}$ and prevented cytoplasmic Ca^{2+} overload. We suggested that $I_{Na,Late}$ could be activated also by nonanthracycline chemotherapeutics (fluoropyrimidines, alkylators, tubulin-active vinca alkaloids) that caused coronary endothelial dysfunction and ischemia,

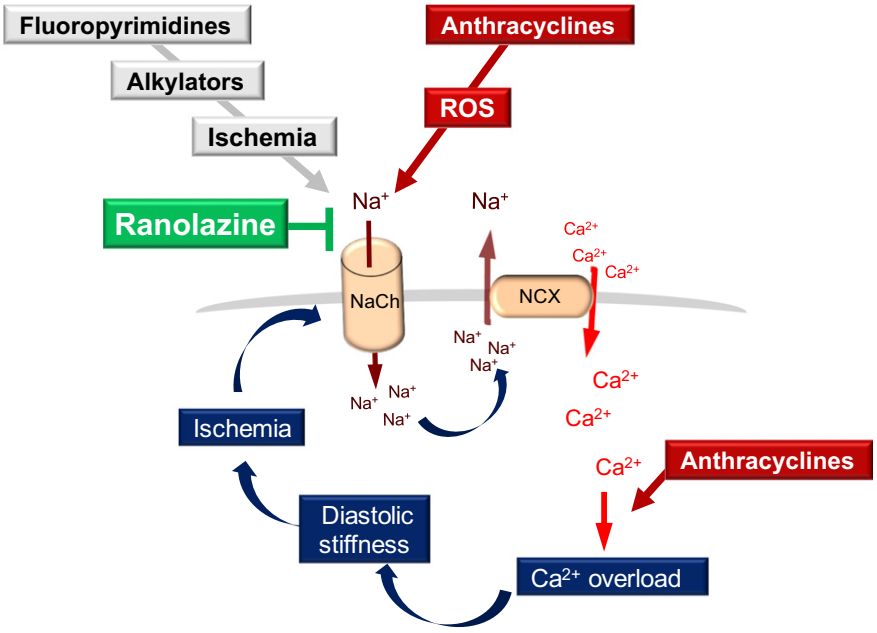

Fig. 2. Ranolazine-inhibitable activation of $I_{Na,Late}$ and increase of diastolic stiffness induced by anthracyclines, alkylators, and fluoropyrimidines. By activating $I_{Na,Late}$ through ROS and ischemia, anthracyclines and nonanthracycline chemotherapeutics cause elevated intracellular Na^+ that exchanges with extracellular Ca^{2+} via the reverse mode Na^+–Ca^{2+} exchanger. Excess Ca^{2+} entry causes diastolic stiffness, and the latter causes ischemia that perpetuates $I_{Na,Late}$ activation. Anthracyclines induce Ca^{2+} overload also by independent mechanisms (increased Ca^{2+} release from sarcoplasmic release and reduced Ca^{2+} sequestration in mitochondria and sarcoplasmic reticulum). By inhibiting $I_{Na,Late}$, ranolazine interrupts these vicious cycles. Modified after ref. [75]. NaCh, Na^+ channel; NCX, Na^+–Ca^{2+} exchanger; ROS, reactive oxygen species.

whether silent or heralded by transient arrhythmias [75]. This latter mechanism would be potentiated if nonanthracycline chemotherapeutics were combined with anthracyclines that activated $I_{Na,Late}$ and caused diastolic dysfunction by their own mechanisms [75]. By inhibiting $I_{Na,Late}$ ranolazine would break vicious cycles initiated by anthracyclines and nonanthracycline chemotherapeutics (Fig. 2).

These premises gave us a rationale to design a Phase 2B study of ranolazine in asymptomatic cancer patients with early diastolic dysfunction. The study was designed to demonstrate that i) asymptomatic diastolic dysfunction could be detected as early as few days after patients completed antitumor therapy ii), 5 week ranolazine treatment relieved protocol-specified indices of diastolic dysfunction, and iii) ranolazine was superior to most common cardiovascular drugs [75]. This study explores the feasibility of secondary prevention with ranolazine. Primary prevention was not explored as we felt that ranolazine, by competing for cytochrome P450 3A and P-glycoprotein, could interfere with metabolization and transport of many antitumor drugs [75]. Once again, cardiovascular interventions must not interfere with optimal oncologic treatment, particularly when cardio-oncologists explore new ideas, new drugs, or new indications for drugs approved in other settings. Patients' recruitment and assessment were completed few months ago, and results are being analyzed for the assessment of ranolazine safety and efficacy.

6. Conclusions

New waves of antitumor drugs will enter clinical practice in the next few years. This will probably cause newer or more severe phenotypes of cardiotoxicity. With new KI, the incidence of cardiac rhythm disturbances (QT prolongation) and blood coagulation disorders (thrombosis, thromboembolism) is very likely to increase. But drugs save lives and hence, cardio-oncologists will be asked to find their best way to protect the cardiovascular system without diminishing oncologic efficacy of new drugs or cocktails of drugs. Excellence in risk:benefit analysis will be a formidable tool to achieve this goal but laboratory scientists too will be crucial for deciphering the molecular foundations of cardiac therapy in cancer patients [83].

Transparency document

The Transparency document associated with this article can be found, in the online version.

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