Pharmacological foundations of cardio-oncology

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NONSTANDARD ABBREVIATIONS: CHF, congestive heart failure; MI, myocardial infarction; HER-2, epidermal growth factor receptor 2; VEGF(r), vascular endothelial growth factor (receptor); TKI(s), small tyrosine kinase inhibitor(s); ROS, Reactive Oxygen Species; LV, left ventricular; LVEF, left ventricular ejection fraction; SHR, spontaneously hypertensive rat; ACEI, angiotensin I converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

RECOMMENDED SECTION ASSIGNMENT: Perspectives in Pharmacology
ABSTRACT

Anthracyclines and many other antitumor drugs induce cardiotoxicity that occurs “on treatment” or long after completing chemotherapy. Dose reductions limit the incidence of early cardiac events but not of delayed sequelae, possibly indicating that any dose level of antitumor drugs would prime the heart to damage from sequential stressors. Drugs targeted at tumor-specific moieties raised hope for improving the cardiovascular safety of antitumor therapies; unfortunately, however, many such drugs proved unable to spare the heart, aggravated cardiotoxicity induced by anthracyclines, or showed safe in selected patients of clinical trials but not in the general population. Cardio-oncology is the discipline aimed at monitoring the cardiovascular safety of antitumor therapies. Although popularly perceived as a clinical discipline that brings oncologists and cardiologists to working together, cardio-oncology is in fact a pharmacology-oriented translational discipline. The cardiovascular performance of cancer survivors will only improve if clinicians joined pharmacologists in the search for new predictive models of cardiotoxicity or mechanistic approaches to explain how a given drug might switch from causing systolic failure to inducing ischemia. The lifetime risk of cardiotoxicity from antitumor drugs needs to be reconciled with the identification of long-lasting pharmacological signatures that overlap with comorbidities. Research on targeted drugs should be reshaped to appreciate that the terminal ballistics of new “magic bullets” might involve cardiomyocytes as innocent bystanders. And finally, the concepts of prevention and treatment need to be tailored to the notion that late onset cardiotoxicity builds on early asymptomatic cardiotoxicity. The heart of cardio-oncology rests with such pharmacological foundations.
Cardiotoxicity of antitumor drugs: Old aspects and new issues

Antitumor drugs have long been known to induce untoward but manageable cardiovascular effects such as transient blood pressure disorders, ischemia, arrhythmias, systolic dysfunction, pericardial effusions. Hormonal treatment of hormone-responsive tumors also introduces a risk of cardiovascular events. There are cases where the cardiac sequelae of antitumor therapies may be life-threatening; for example, cumulative doses of antibiotics like anthracyclines, mitomycin, or mitoxantrone, induce dilative cardiomyopathy and congestive heart failure (CHF) (Minotti et al., 2004; Menna et al., 2008).

Almost all of the approved antineoplastics have been shown to induce some type of cardiotoxicity (see Table I for a representative list of cardiotoxic drugs). With that said, the clinical manifestations of cardiotoxicity seem to have changed in the last years. Reducing the cumulative dose of anthracyclines (topoisomerase II inhibitors and DNA intercalators) was of help in diminishing acute or subacute cardiotoxicity but not chronic cardiotoxicity that occurred five or more years after completing chemotherapy; moreover, some cancer survivors developed CHF while others developed ischemic disease and myocardial infarction (MI) (Carver et al., 2007; Swerdlow et al., 2007). Nonanthracycline chemotherapeutics ( antimetabolites, alkylators, tubulin-active agents, or other topoisomerase II inhibitors like etoposide) were known to induce systolic dysfunction but also, if not primarily, ischemia that occurred within hours or days from treatment (Menna et al., 2008); however, the available evidence now shows that also nonanthracycline chemotherapeutics introduce a lifetime risk of cardiotoxicity (Carver et al., 2007). The importance of age of first treatment has been reappraised. Children-adolescents and the elderly had long been considered to be more vulnerable by anthracyclines, but recent studies show that late onset cardiotoxicity could occur independent of age of first treatment (Swerdlow et al., 2007).

Cardiotoxicity is induced by antibodies or small molecules targeted at growth factors, or their receptors, or receptor-associated kinases. Receptors thought to be crucial to tumor cells (like e.g., the epidermal growth factor receptor 2, HER-2) are expressed in cardiomyocytes too and relay a number of survival signals (Cheng and Force, 2010). Blocking HER-2 with the antibody trastuzumab therefore precipitates cardiotoxicity from concomitant anthracyclines or causes
dysfunction in patients with a prior exposure to anthracyclines (Menna et al., 2008). Antibodies or small tyrosine kinase inhibitors (TKIs) targeted at the Vascular Endothelial Growth Factor (VEGF) or its receptors (VEGFRr) may cause hypertension, contractile dysfunction, ischemia (Schmidinger et al., 2008). Imatinib and other TKIs of Bcr-Abl and C-Kit of leukaemic or gastrointestinal sarcoma cells are also suspected to cause cardiotoxicity (Cheng and Force, 2010).

**What is cardio-oncology?**

Concerns about cardiotoxicity from antitumor drugs should be weighed against survival or curability benefits; for example, anthracyclines caused lifesaving effects that outweighed the risk of cardiac-related death at 10 or 20 years of follow-up (Gianni et al., 2008). Less is known about the recently developed targeted drugs. Studies with short follow-up demonstrate that commencing trastuzmab after chemotherapy improved the event-free survival of women with HER-2\(^+\) breast cancer, antiangiogenic drugs were active in many advanced tumors, imatinib was both lifesaving in chronic myeloid leukemia and active in otherwise untreatable gastrointestinal sarcomas (Albini et al., 2010; Cheng and Force, 2010; Suter et al., 2007). These facts show that cancer patients should not be denied the benefits from drugs with known or suspected cardiotoxicity; similar concepts apply to the elderly too (Carver et al., 2008). With that said, cardiotoxicity compromises the quality of life and calls for costly medical assistance. Oncologists and cardiologists therefore were asked to jointly assess the risk:benefit of antitumor therapies and to identify the best possible cardiac surveillance or preventative measures that improved the therapeutic index of antitumor therapies. This is the clinical dimension of cardio-oncology (Cardinale et al., 1996; Gianni et al., 2008), sometime referred to as onco-cardiology (Albini et al., 2010).

Confining cardio-oncology to the merging of cardiology with oncology would be an unforgivable oversight: cardio-oncology is a much broader discipline that goes from bench to bedside and builds clinical initiatives on pharmacological reasonings. Here we briefly highlight some contemporary issues that illustrate the pharmacological foundations of cardio-oncology.
Lifetime risk of cardiotoxicity: A matter of long-lasting pharmacological signatures

There is an unmet need for deciphering the lifetime risk of cardiotoxicity; this would be much important for drugs, like the anthracyclines, that are cleared from the heart quite rapidly and decrease to below levels of toxic concern (Salvatorelli et al., 2009).

In rats the anthracycline doxorubicin acutely impaired cardiac oxidative phosphorylation; this was followed by formation of reactive oxygen species (ROS) that caused both quantitative and qualitative alterations of mitochondrial DNA and its encoded respiratory chain subunits. Inasmuch as mitochondrial dysfunction persisted and worsened after completing anthracycline treatment, these studies suggested that the lifetime risk of cardiotoxicity could be caused by a mitochondrionopathy that self-maintained in the absence of continued exposure to doxorubicin (Lebrecht and Walker, 2007). In humans, however, mitochondrionopathy did not correlate with cardiotoxicity induced by other anthracyclines. Post-mortem studies of hearts from cancer patients showed that mitochondrionopathy was caused by doxorubicin but not by its analogue, epirubicin (Lebrecht and Walker, 2007), in spite of that epirubicin retained ≥60% of the cardiotoxic potential of doxorubicin (Menna et al., 2008).

The lifetime risk of cardiotoxicity from anthracyclines could be better explained by their conversion to secondary alcohol metabolites. Being more polar than their parent drugs, such metabolites are poorly cleared from cardiomyocytes and accumulate to becoming a long-lasting anthracycline signature in the heart (Minotti et al., 2004; Menna et al., 2008); moreover, secondary alcohol metabolites are many times more potent than their parent anthracyclines at inactivating Ca\(^{2+}\) handling proteins of the contraction-relaxation cycle (Minotti et al., 2004) or key regulators of energy metabolism and redox balance, such as cytoplasmic aconitase (Minotti et al., 1998; Cairo et al., 2002). Secondary alcohol metabolites therefore cause cardiotoxicity both during chemotherapy and long after ending it. The levels of alcohol metabolite formation correlated with clinical cardiotoxicity from different anthracyclines. Experiments with ex vivo human myocardial samples exposed to anthracyclines in vitro showed that both doxorubicin and epirubicin were converted to secondary alcohol metabolites but epirubicin formed ~50 less alcohol metabolite than doxorubicin did (Salvatorelli et al., 2006; Salvatorelli et al., 2007; Salvatorelli et al., 2009).
Anthracyclines are not the only drugs that release long-lasting signatures of cardiotoxicity. Testicular cancer survivors with a history of treatment with the alkylating agent, cisplatin, carry an increased risk for MI (Carver et al., 2007). In these subjects the plasma levels of cisplatin remain measurable up to 20 years after ending therapy, causing cumulative dysfunction of endothelial cells that eventually detach from the intima of vessels (Vaughn et al., 2008). A long-lasting pharmacological signature (circulating cisplatin) therefore correlates with molecular mechanisms of damage (endothelial dysfunction) and clinical facts (risk of MI).

Other chemotherapeutics seem to lack long-lasting signatures in spite of their proven or suspected implication in late onset cardiotoxicity. This calls for ad hoc studies and changing strategies in drug development: new chemical entities should be routinely scrutinized for long-lasting pharmacological signatures that primed cancer survivors to cardiotoxicity.

Drugs are not alone: The multiple-hit hypothesis

Roughly half of all childhood cancer survivors with a history of anthracycline treatment showed asymptomatic cardiac dysfunction at non invasive tests; however, symptomatic events only occurred in ~5% of them (Mulrooney et al., 2009). Similar concepts apply to adult onset cancer survivors with a history of anthracycline treatment (Hequet et al., 2004). On the other hand, circulating cisplatin would be seen in the vast majority of testicular cancer survivors, but MI only occurred in ≤6% of them (van den Belt-Dusebout et al., 2006). Although still consistent with higher hazard ratios for cardiac events in cancer survivors as compared to age-matched siblings or other subjects from the general population, these figures denote that the incidence of cardiotoxicity might be influenced by interpatient variability.

Some patients might retain stronger pharmacological signatures of cardiotoxicity as compared with others. Gain of function V244M polymorphism of carbonyl reductases 3, one of the many reductases that could convert anthracyclines to secondary alcohol metabolites, was retrospectively associated with an increased risk of CHF in long-term survivors of childhood cancer (Blanco et al., 2008). Interestingly, however, experiments with ex vivo human myocardial samples exposed to anthracyclines in vitro showed that carbonyl reductases metabolized some
anthracyclines (daunorubicin) but not others (doxorubicin, epirubicin); the latter were much better substrates of aldehyde reductases belonging to the superfamily of aldo-keto reductases (Menna et al., 2008; Salvatorelli et al., 2007). Thus, carbonyl reductase polymorphisms would be important in childhood cancer survivors who had received daunorubicin for the treatment of e.g., acute lymphoblastic leukemias, but not in survivors who had received doxorubicin for the treatment of sarcomas or other malignancies. For analogous reasons carbonyl reductase polymorphisms would not explain interpatient variability among survivors who received doxorubicin or epirubicin rather than daunorubicin for adult onset breast cancer or lymphomas. With regard to cisplatin, pharmacokinetic studies showed that for any given body surface-based dose level there was a 3-fold interpatient variability in the plasma exposure to cisplatin (Peng et al., 1997). Patients who developed higher plasma cisplatin levels during chemotherapy might be considered to carry such higher levels also after ending chemotherapy, yet, there is a paucity of studies that explored cause-and-effect relations between acute or chronic levels of cisplatin and the risk of late onset cardiotoxicity.

Absent universal markers for the lifetime risk of cardiotoxicity, one should look at cardiotoxicity from alternative but not mutually exclusive viewpoints. Preexisting comorbidities or unfavourable lifestyle choices (hypertension, diabetes, hyperlipidemia, reduced physical activity) have long been known to increase the risk of cardiotoxicity in patients scheduled to receiving chemotherapy (Minotti et al., 2004). The available evidence suggests that this picture should be viewed the other way around: in comparison with age-matched controls, previously healthy cancer survivors developed more comorbidities or tended to reducing physical activity (De Bruin et al., 2009; Jones et al., 2007; Vaughn, 2008). It follows that asymptomatic, potentially reversible cardiotoxicity from “safe doses” of anthracyclines or nonanthracycline chemotherapeutics may progress to symptomatic events by overlapping with risk factors that matured after ending chemotherapy. This is the so-called multiple-hit hypothesis, according to which late onset cardiotoxicity builds on pharmacological and non pharmacological sequential injuries (Jones et al., 2007; Menna et al., 2008). These concepts calls for new approaches to the caring of cancer
survivors: in these subjects comorbidities or unfavourable lifestyle choices should be prevented or treated more vigorously than in the general population.

From antitumor drugs to diastolic dysfunction and more

Asymptomatic diastolic dysfunction fingerprints many cancer survivors (Gianni et al., 2008). Anthracyclines cause diastolic elevated [Ca^{2+}]; and left ventricular (LV) wall stiffness (diastolic dysfunction) by a number of mechanisms (Minotti et al., 2004). Diastolic stiffness then increases interstitial pressure and diminishes coronary conductance, eventually inducing ischemia that further increases [Ca^{2+}]; and stiffness by its own mechanisms. Nonanthracycline chemotherapeutics would trigger this vicious cycle through ischemia due to endothelial dysfunction and/or coronary spasm (Menna et al., 2008).

Reciprocal interactions between diastolic dysfunction and ischemia need to be brought centerstage. Nonanthracycline chemotherapeutics that caused persistent endothelial dysfunction, and hence ischemia, would induce diastolic dysfunction that aggravated ischemia. Such reciprocal interactions may remain asymptomatic for many years; accordingly, diastolic dysfunction at noninvasive tests preceded MI in testicular cancer survivors with a history of cisplatin-based therapy (Altena et al., 2009). Patients treated with anthracyclines and chemotherapeutics that only caused transient endothelial dysfunction or coronary spasm (like the tubulin-active vinca alkaloid, vincristine, or the glycopeptide antibiotic, bleomycin) would be exposed to a blending of diastolic dysfunction and ischemia that made diastolic stiffness and reduced coronary conductance develop stronger and more persistent; accordingly, the risk of MI in previously nonischemic Hodgkin's lymphoma survivors correlated with their prior exposure to anthracyclines in combination with vincristine and/or bleomycin (Swerdlow et al., 2007). Diastolic dysfunction and reduced coronary conductance would render the heart more vulnerable by comorbidities that diminished coronary flow or increased oxygen demand, like e.g. premature atherosclerosis or hypertension.

Radiotherapy feeds in this context: mediastinal irradiation causes diastolic dysfunction and premature coronary artery disease in cancer survivors (Carver et al., 2007).
Different mechanisms may govern the switching of diastolic dysfunction to systolic failure. Anthracyclines cause reduced expression and/or increased disorganization of myofibrils, induce apoptosis, and trigger LV hypertrophy that deteriorates to wall thinning and dilation because of chronically unbalanced afterload (Gianni et al., 2008). Absent a synergism of anthracyclines with factors promoting diastolic dysfunction, the equilibrium would be pushed toward systolic failure. HER-2 protects against myofibrillar disorganization and serves a number of antiapoptotic functions (Cheng and Force, 2010; Pentassuglia et al., 2009); it follows that blocking HER-2 would accelerate progression to systolic failure. Breast cancer women who received trastuzumab in combination with “safe doses” of anthracyclines therefore developed dilative cardiomyopathy and systolic failure rather than MI. Administering trastuzumab after anthracyclines diminished the severity of cardiotoxicity but not its clinical phenotype: systolic dysfunction, though reversible and manageable, prevailed over ischemic disease (Suter et al., 2007).

In clinical practice cancer patients or survivors are monitored by serial measurements of left ventricular ejection fraction (LVEF). Pharmacological notions suggest that this would be inadequate to capture the blending of diastolic dysfunction with systolic failure or ischemia (Figure 1). New imaging techniques should be adopted and tailored to the characteristics of patients and chemotherapy regimens.

**Targeted drugs are not magic bullets**

More than 1000 drugs are being developed by pharmaceutical companies to target tyrosine kinases or, to a lesser extent, serine-threonine kinases that are crucial to tumor growth; meanwhile, reports or concerns about cardiotoxicity from the approved targeted drugs accumulate steadily. Thus, both hopes and fears dominate the field of targeted therapies.

Cardiotoxicity from targeted drugs is often said to occur “unexpectedly” (De Keulenaer et al., 2010). Pharmacologists would perceive this as an oversimplification. As long as a molecular entity governed cardiac development or maintained expression levels in the postnatal heart, targeting that particular entity would cause cardiotoxicity quite predictably. Defective expression of VEGF caused embryonic death that was accompanied by prominent cardiac malformations (Bi et
al., 1999); genetic deletion of HER-2 caused cardiac embryonic death (Lee et al., 1998). Either information was available before bevacizumab and trastuzumab were shown to cause cardiotoxicity in cancer patients. The next few years will witness global development of drugs targeted at many other biological moieties. Cardiotoxicity from new agents should be said to occur "predictably" if a given molecular target participated in one or more cardiac functions.

Research on targeted drugs is also biased by the assumption that modelling a TKI to a given kinase or an intended number of kinases would minimize the risk of targeting other kinases; hence, cardiac toxicity that was caused by any such designed TKI would be liable to interpretation and proper treatment. Pharmacologists would perceive this as a case of overt enthusiasm. Sunitinib was thoughtfully designed as a multikinase inhibitor that targeted VEGFr, platelet-derived growth factor α/β, colony-stimulating factor 1 receptor, FMS-related tyrosine kinase 3, and few other kinases; however, the available evidence shows that at therapeutic plasma levels sunitinib would inhibit some 90 kinases. Inhibition of which kinase or combination of kinases caused cardiotoxicity from sunitinib would be very difficult to ever identify. Almost all of the approved TKIs bind to more kinases, albeit with different $K_d$ values; cardiotoxicity from TKIs therefore correlated with such a lack of target specificity (Hasinoff, 2010).

As it was said before, trastuzumab worsened cardiotoxicity from concomitant anthracyclines but trastuzumab administered after anthracyclines caused reversible systolic dysfunction that only occasionally accompanied with ultrastructural changes typical of anthracycline cardiotoxicity. This and other factors provided a rationale for distinguishing type 1 cardiotoxicity (induced by anthracyclines) from type 2 cardiotoxicity (induced by trastuzumab) (Ewer and Lippman, 2005). Other targeted drugs might fit in type II cardiotoxicity. With that said, one cannot ignore that targeted therapies cause more cardiotoxicity in the general oncologic population than in selected patients of clinical trials: this occurs with angiogenesis inhibitors (Schmiderger et al., 2008), it probably occurs with trastuzumab to some extent (Menna et al., 2008), it remains under scrutiny for imatinib and cogeners and dual TKIs of HER-1/HER-2 like lapatinib (see also Table I). It therefore seems that comorbidities influenced cardiotoxicity from targeted therapies the same way as they influenced cardiotoxicity from old generation chemotherapeutics, presumably because
elimination of growth and survival factors by the targeted drugs made the heart more vulnerable by hemodynamic or metabolic stress. Furthermore, early clinical experience showed that cardiotoxicity from targeted drugs may move beyond contractile dysfunction or ischemia: angiogenesis inhibitors and lapatinib cause QT prolongation that might put patients at risk for torsade de pointes and sudden death (Menna et al., 2008).

Targeted therapies have been around for few years only; the epidemiologic dimension of cardiotoxicity from these drugs, whether in isolation or in concert with comorbidities, will need to be defined at longer periods of follow-up. With these concerns in mind, it would be wise surrendering to the concept that there are no magic bullets that cured a patient without engaging dangerous liasons with the cardiovascular system or comorbidities. Pharmacologists would better serve cancer patients and survivors by predicting the risk of cardiotoxicity or by elucidating means for preventing or treating it.

Need for better preclinical models and clinical trials

There is an unmet need for preclinical models that predicted the risk of cardiotoxicity from antitumor drugs. Studies with ex vivo human myocardial samples exposed to anthracyclines in vitro helped to define the enzymology and pharmacokinetics of secondary alcohol metabolites (Salvatorelli et al., 2007; Salvatorelli et al., 2009); however, this model could not explore the pathobiology of the “multiple-hit hypothesis”. Animal models of chronic cardiotoxicity are limited by heterogeneous drug metabolism such that the enzymology and net levels of anthracycline secondary alcohol metabolites would be quite different from those of human heart (Minotti et al., 2004); moreover, animal models require weeks of treatment and weeks or months of observation, but in the absence of comorbidities only few animals would develop cardiac abnormalities (Gianni et al., 2008). The spontaneously hypertensive rat (SHR) shows a greater sensitivity to chronic anthracycline treatment and develops functional, histologic, and biochemical aspects of cardiotoxicity that more closely resembles those of cancer patients (Herman et al., 1985); however, SHR models would be biased by the same metabolic pitfalls as those of normotensive rats, confounding an interpretation of the cause-and-effect relations between the cardiac levels of
secondary alcohol metabolites and their toxic synergism with hypertension. An alternative but not mutually exclusive approach would be to treat SHR with both anthracyclines and nonanthracycline chemotherapeutics, thereby reproducing clinical conditions where diastolic dysfunction from one drug interacted with ischemia from another drug; unfortunately, there is a lack of studies in that direction.

Animal models do not always anticipate the risk of cardiotoxicity from targeted drugs. Trastuzumab did not recognize the ectodomain of HER2 in the murine heart and hence, it lacked cardiotoxicity in preclinical studies (Pegram et al., 2006). Mice treated with sunitinib developed cardiomyocyte apoptosis but this only occurred after inducing hypertension with a sympathicomimetic agents (Cheng and Force, 2010): this denotes that VEGF-VEGFr signalling regulates capillary density and helps the cardiovascular system to withstand hemodynamic load (Schmidinger et al., 2008). There is a lack of models that explored the capability of sunitinib to cause hypertension and then cardiotoxicity by its own.

Clinical trials may underestimate the risk of cardiotoxicity from antitumor drugs: phase III studies exclude or only marginally include patients with risk factors, cardiac surveillance almost invariably rests with LVEF measurements only, follow-up may be too short to predict late onset cardiotoxicity due to sequential stressors. Pharmacological reasonings call for proof-of-concept trials in which patients were stratified by risk factors and were probed for asymptomatic dysfunction(s) precursor to late onset cardiotoxicity.

**Reshaping prevention and treatment**

For many years dexrazoxane was synonymous to preventing anthracycline cardiotoxicity. Formally labelled as iron chelator, dexrazoxane was thought to diminish formation of anthracycline-iron complexes that generated ROS in excess of the antioxidant defences of cardiomyocytes. This mechanism has been questioned in recent years; perhaps more importantly, clinical use of dexrazoxane has been limited by unconfirmed concerns that it could also diminish anthracycline activity in tumors (Gianni et al., 2008; Menna et al., 2008). Absent regulatory or educational initiatives to resuscitate dexrazoxane’s popularity, anthracycline cardiotoxicity can be prevented by
replacing rapid infusions with slow infusions or liposomal formulations that, by different mechanisms, diminish the cardiac uptake of anthracyclines (Minotti et al., 2004); unfortunately, many doctors perceive these procedures as too expensive or laborious.

The concepts of prevention and treatment clearly need to be reshaped. The notion that late onset cardiotoxicity develops over months or years through asymptomatic cardiac dysfunction suggests that drugs used “to treat” symptomatic events should be used earlier “to prevent” subclinical damage. In limited studies prophylactic commencement of β blockers or angiotensin I converting enzyme inhibitors (ACEI) prevented systolic dysfunction induced by cumulative doses of chemotherapeutics (Kalay et al., 2005; Cardinale et al., 2006), as one would expect from the known effects of such drugs on reducing heart rate and afterload. Interestingly, however, there may be other mechanisms for the preventative efficacy of β blockers and ACEI (or angiotensin II receptor blockers, ARB). Catecholamines and angiotensin II downregulate endothelial expression of neuregulin 1, that is the ligand promoting heterodimerization of HER-2 with HER-4 and activation of salvage pathways downstream of HER-2 (Lemmens et al., 2006). By shielding endothelial cells from catecholamines or angiotensin II both β blockers and ACEI (or ARB) would indirectly upregulate neuregulin-1 expression, making cardiomyocytes more resistant to hemodynamic and chemical stress.

Prophylactic commencement of cardiovascular drugs is uncommon outside of exploratory studies, doctors believe that cancer patients with normal cardiac function should not be exposed to discomfort possibly caused by such drugs. These concerns should be weighed against the notion that delayed commencement of ACEI would only transiently affect the progression of chemotherapy-related cardiomyopathy (Gianni et al., 2008); moreover, experimental evidence suggests that progressive cardiomyopathy might be accompanied by functional uncoupling of HER-2 activation from downstream survival signals, making β blockers and ACEI (or ARB) less protective (Doggen et al., 2009). With the possible exception of conditions where oncologists may need a persistent blockade of HER-2 and microvasculature-derived signals for optimal control of tumor growth, the balance of evidence would favour the earliest possible commencement of cardiovascular medications.
The building of late onset systolic failure or ischemia on earlier asymptomatic diastolic dysfunction calls for pharmacological interventions specific to diastolic LV stiffness. In patients with chronic diastolic dysfunction (that is heart failure with preserved LVEF) nitrates and diuretics are indicated for reducing fluid retention and cardiac filling pressure. The efficacy of β blockers is controversial; recent evidence suggests that nebivolol could be better than others, presumably because of its corollary effects on improving endothelial dysfunction through antioxidative properties and functional coupling of nitric oxide synthase (Kamp et al., 2010). Research on drugs that specifically prevented or mitigated diastolic LV stiffness (lusitropic agents) should nonetheless be considered a priority in the next coming years.

Pharmacology and the future of cardio-oncology

We described how cardiotoxicity from antitumor drugs has changed in the past years. Asymptomatic cardiotoxicity (contractile dysfunction or ischemia) is an increasingly frequent consequence of antitumor therapies; absent early cardiovascular medications, asymptomatic cardiotoxicity synergizes with multiple hits and progresses toward late onset cardiac events (Figure 2). New waves of antitumor drugs will make cardiotoxicity change even faster in the next coming years. The vulnerability of the heart as a paracrine intercellular system anticipates the occurrence of new cardiotoxicity phenotypes caused by e.g., interruption of cross talks between the cardiac microvasculature and myocytes (De Keulenaer et al., 2010). The next few years will also witness research on cardiac progenitor cells that repopulate foci of myocyte damage. Progenitor cells succumb to anthracyclines (De Angelis et al., 2010) but little is known about their vulnerability by targeted drugs. This calls for ad hoc studies, as targeting progenitor cells would prime cancer survivors to inefficient myocardial repopulation.

Cardiologists and oncologists will be asked to manage new paradigms of cardiotoxicity, but mechanistic insight and therapeutic readouts will only come from pharmacological research. The heart of cardio-oncology will rest with pharmacological foundations.
REFERENCES


FOOTNOTES

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LEGENDS FOR FIGURES

Figure 1  Diastolic dysfunction bridges anticancer therapies to ischemia or systolic failure

Anthracyclines or mediastinal irradiation cause diastolic dysfunction that induces ischemia or aggravates with ischemia induced by other chemotherapeutics. HER-2 blockade facilitates progression of diastolic dysfunction to systolic failure. See also text for explanations.

Figure 2  Early cardiovascular medications and cardiac safety vs multiple hits and late onset cardiac events

Asymptomatic cardiotoxicity may be induced by anthracyclines, nonanthracycline chemotherapeutics, targeted drugs, in concert with polymorphisms or mediastinal irradiation. Early commencement of cardiovascular medications pushes asymptomatic cardiotoxicity toward cardiac safety. Absent such medications asymptomatic cardiotoxicity synergizes with multiple hits (comorbidities, other stressors) and progresses toward late onset events. See also text for explanations.
Table I
Antitumor drugs with known, likely, or presumed cardiotoxicity

<table>
<thead>
<tr>
<th>Anthracyclines and nonanthracycline antibiotics</th>
<th>Nonanthracycline chemotherapeutics</th>
<th>Targeted drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>anthracyclines (doxorubicin, epirubicin, daunorubicin, idarubicin)</td>
<td>alkylation agents (cyclophosphamide, ifosfamide, cisplatin, busulfan)</td>
<td>anti-HER-2 (trastuzumab) anti-HER-2/HER-1 (lapatinib)</td>
</tr>
<tr>
<td>nonanthracycline antibiotics (mitoxantrone, bleomycin, mitomycin)</td>
<td>tubulin-active agents (vinca alkaloids: vincristine, vinblastine) (taxanes: paclitaxel, docetaxel)*</td>
<td>anti-VEGF (bevacizumab) anti-VEGF (sunitinib, sorafenib)</td>
</tr>
<tr>
<td></td>
<td>antimetabolites (fluoropyrimidines, methotrexate, fludarabine, cytarabine)</td>
<td>anti-Bcr/Abl, anti-C-Kit (imatinib, dasatinib, nilotinib)</td>
</tr>
<tr>
<td></td>
<td>topoisomerase II inhibitors (etoposide)</td>
<td></td>
</tr>
</tbody>
</table>

*Cardiotoxicity is caused also by hypersensitivity reactions to vehicle, particularly in the case of paclitaxel; taxanes may aggravate anthracycline-related cardiotoxicity.

Based on Albini et al., 2010, Carver et al., 2007, Cheng and Force, 2010, Menna et al., 2008.
Figure 1
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