Pharmacology at work for cardio-oncology:
Ranolazine to treat early cardiotoxicity
induced by antitumor drugs

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NONSTANDARD ABBREVIATIONS: HF, heart failure; MI, myocardial infarction; LV, left ventricle; LVEF, left ventricle ejection fraction; ROS, reactive oxygen species; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; I_{Na,Late}, late inward sodium current; BNP, B-type natriuretic peptide; Nt-proBNP, inactive aminoterminal fragment of B-type natriuretic peptide; Tn, troponin.

RECOMMENDED SECTION ASSIGNMENT: Perspectives in Pharmacology
ABSTRACT

Antitumor drugs may cause asymptomatic diastolic dysfunction that introduces a lifetime risk of heart failure or myocardial infarction. Cardio-oncology is the discipline committed to the cardiac surveillance and management of cancer patients and survivors; however, cardio-oncology teams do not always attempt to treat early diastolic dysfunction. Common cardiovascular drugs, such as β blockers or angiotensin converting enzyme inhibitors or others, would be of uncertain efficacy in diastolic dysfunction. This perspective describes the potential value of ranolazine, an antianginal drug that improves myocardial perfusion by relieving diastolic wall tension and dysfunction. Ranolazine acts by inhibiting the late inward sodium current, and pharmacological reasonings anticipate that antitumor anthracyclines and nonanthracycline chemotherapeutics might well induce anomalous activation of this current. These notions formed the rationale for a clinical study of the efficacy and safety of ranolazine in cancer patients. This study was not designed to demonstrate that ranolazine reduced the lifetime risk of cardiac events; it was designed as a short term proof-of-concept study that probed the following hypotheses: i) asymptomatic diastolic dysfunction could be detected few days after patients completed antitumor therapy, ii) ranolazine was active and safe in relieving echocardiographic and/or biohumoral indices of diastolic dysfunction, measured at five weeks or six months of ranolazine administration. These facts illustrate the translational value of pharmacology, which goes from identifying therapeutics opportunities to validating hypotheses in clinical settings. Pharmacology is a key to the success of cardio-oncology.
Introduction

Cardio-oncology is the discipline that cares of the heart of cancer patients; in fact, conventional chemotherapeutics and some of the newer “targeted” drugs may cause cardiovascular toxicities that call for preventive or curative measures (Minotti et al, 2010). Cardio-oncology rests with an in-depth understanding of the mechanisms of cardiotoxicity and a good collaboration between oncologists and cardiologists. Unfortunately, the mechanisms of toxicity are only in part understood, and the timing and appropriateness of cardiovascular medications in cancer patients remain highly debated. Pharmacologists may help cardiologists and oncologists by providing mechanistic insight and by identifying cardiovascular drugs that proved safe and effective in patients at risk for cardiotoxicity. This perspective describes how pharmacological reasonings identified ranolazine as a valuable option and formed the rationale for a proof-of-concept Phase IIB study with this drug.

General concepts on cardiotoxicity from antitumor drugs

Doxorubicin and other anthracyclines induce both acute and chronic cardiotoxicity. Acute cardiotoxicity occurs shortly after initiation of an anthracycline regimen and consists of arrhythmias, hypotension, mild depression of contractile function. Acute cardiotoxicity is relatively infrequent and usually reversible. In contrast, chronic cardiotoxicity develops in a dose-related manner and manifests as potentially life-threatening cardiomyopathy and heart failure (HF) (Minotti et al., 2004). Nonanthracycline chemotherapeutics (alkylators, antimetabolites, tubuline-active agents) may cause coronary endothelial dysfunction and spasm which manifest as ischemia or arrhythmias, but the dose-dependence of such events is less obvious. Targeted agents (antibodies, kinase inhibitors) tend to induce transient cardiac dysfunction, but some of them may render the heart more vulnerable by anthracyclines. With inhibitors of angiogenesis, cardiotoxicity is aggravated by class-related effects like microvasculature dysfunction, hypertension, thromboembolism (Kamba and McDonald, 2007; Schmidinger et al., 2008). Mechanisms and manifestations of cardiotoxicity
from conventional chemotherapeutics or newer drugs have been reviewed elsewhere (Lal et al., 2013; Menna et al. 2012; Suter et al., 2013).

**Cardiotoxicity and the risk:benefit of antitumor drugs**

In patients without preexisting cardiovascular risk factors, cumulative doses of 400 mg doxorubicin/m² introduce a 5% risk of HF (Swain et al., 2003). Cumulative doses of 240-360 mg of doxorubicin/m² cause much lower risk but retain life-saving effects (Gianni et al., 2008). More than three million Americans are entering their fifth to tenth year of survival since cancer diagnosis, and many of them received low dose anthracycline regimens (American Cancer Society, 2012). Nevertheless, studies of breast cancer survivors show that HF may develop five to ten years after completing chemotherapy (Pinder et al., 2007). Studies of long term childhood cancer survivors show that >250 mg of anthracycline/m² was high enough to increase the lifetime risk of HF (Mulrooney et al., 2009), while 100 mg of anthracycline/m² was high enough to cause asymptomatic cardiac dysfunction (Hudson et al., 2007). Survivors of childhood or adult cancer also show higher incidence of myocardial infarction (MI), which correlates with exposure to anthracyclines (Minotti et al., 2010). These observations suggest that there is no completely “safe” dose of anthracyclines in children (Barry et al., 2007) or adults (Menna et al., 2012). In other studies the risk of delayed MI correlated with patient’s exposure to alkylators like platinum (Altena et al., 2009) or tubuline-active agents like vincristine (Swerdlow et al., 2007). All such findings denote that with current treatment protocols, anthracyclines and nonanthacycline chemotherapetics are life-saving but introduce a lifetime risk of cardiac events.

**Antitumor drugs and early diastolic dysfunction**

Asymptomatic cancer survivors often present echocardiographic indices of diastolic dysfunction characterized by altered relaxation or restrictive pattern (stiffness) (Altena et al, 2009; Carver et al., 2007). In non-oncologic settings, persistent altered relaxation or stiffness cause left ventricle (LV) remodelling that makes diastolic dysfunction progress to HF with preserved left ventricle ejection (LVEF) and eventually, to HF with reduced LVEF (Borlaug and Paulus, 2011). Diastolic dysfunction can also cause and be caused by ischemia. Myocardial stiffness and remodelling increase interstitial pressure and diminish coronary conductance, eventually inducing...
ischemia that aggravates myocardial stiffness by cytoplasmic Ca\textsuperscript{2+} overload and other mechanisms (Hale et al., 2008). In oncologic settings, the progression of cardiotoxicity from asymptomatic diastolic dysfunction to HF or ischemic disease may be driven by several factors. Cancer survivors are more susceptible to develop comorbidities that induce or aggravate diastolic dysfunction (hypertension, diabetes, dyslipidemia) (Armstrong et al., 2012). It follows that asymptomatic diastolic dysfunction may progress toward HF or ischemic disease by synergizing with risk factors (“hits”) that matured after completing chemotherapy. Unintentional hits may also come from targeted therapies or mediastinal irradiation that were administered concomitant with, or after chemotherapy. The so-called “multiple hits hypothesis of cardiotoxicity” recapitulates such a broad spectrum of possibilities (Menna et al., 2008).

**Unmet needs: Drugs against diastolic dysfunction and proof-of-concept studies**

The available evidence suggests that diastolic dysfunction could be detected a few months after ending chemotherapy (Tassan-Mangina et al., 2006), but the possibility that it developed early during the course of chemotherapy was not investigated. This calls for proof-of-concept studies that characterized diastolic dysfunction as the earliest consequence of antitumor therapies and probed drugs that could safely prevent it.

Dexrazoxane is the only drug approved for preventing anthracycline-related cardiotoxicity. Dexrazoxane chelates redox-active iron and can also divert topoisomerase IIβ from causing DNA double-strand breaks associated with altered mitochondrial biogenesis and function. In either case, dexrazoxane diminished formation of reactive oxygen species (ROS) in the relatively unprotected heart (Lyu et al., 2007; Menna et al., 2012; Zhang et al., 2012). Clinical use of dexrazoxane has been limited by unconfirmed reports that it could interfere with anthracycline activity in tumors (Swain et al., 2007); therefore, current guidelines recommend using dexrazoxane only in patients who received 300 mg of doxorubicin/m\textsuperscript{2} and may benefit from continued anthracycline treatment (Schuchter et al., 2002).

Common cardiovascular drugs (β blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), Ca\textsuperscript{2+} antagonists) prevented chemotherapy-induced LVEF decreases in some limited studies, but this reflected their ability to reduce heart
rate-pressure products rather than their ability to prevent an earlier diastolic dysfunction (Menna et al., 2012). Many doctors also believe that discomforts from chemotherapy (fatigue, nausea, vomiting) should not be aggravated by discomforts from β blockers, ACEI, ARB, or Ca\textsuperscript{2+} antagonists (bradycardia, hypotension, cough, fluid retention). There is an unmet need for drugs that acted on diastolic dysfunction in a specific manner (Paulus and van Ballegoij, 2010).

**Ranolazine**

The orally available piperazine derivative, ranolazine, was approved by the Food and Drug Administration as first-line or top-on-therapy agent for the treatment of stable angina; in Europe, ranolazine was approved for the treatment of stable angina in patients who are inadequately controlled by, or intolerant to other antianginal drugs (β-blockers, ACEI, ARB, calcium antagonists). Ranolazine reduces angina episodes, nitrate consumption, uptitration of other antianginal drugs, and importantly, it does so without reducing heart rate-pressure products (Stone, 2008).

In ischemia-reperfusion or anoxia-reoxygenation, fatty acid oxidation prevails over glucose oxidation and causes decreased recovery of cardiac energy during reperfusion. Ranolazine was originally believed to protect the heart by inhibiting fatty acid oxidation and by shifting metabolism toward glucose oxidation; in preclinical models, however, inhibition of fatty acid oxidation occurred at concentrations of ranolazine that were much higher than those associated with the beneficial effects of ranolazine in ischemia/reperfusion or anoxia/reoxygenation (≥100 µM vs ≤20 µM, respectively) (MacInnes et al., 2003; Matsumura et al., 1998). The preponderance of evidence now shows that ranolazine acts by inhibiting the late inward sodium current (I\textsubscript{Na,Late}) (Belardinelli et al., 2006; Hale et al., 2008).

In the repolarizing ischemic LV there is delayed and/or incomplete inactivation of I\textsubscript{Na,Late}. This causes elevation of intracellular Na\textsuperscript{+}, which exchanges with extracellular Ca\textsuperscript{2+} via the reverse mode Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger. Excess Ca\textsuperscript{2+} entry activates myofilaments, increases diastolic wall tension, and reduces coronary conductance (Hale, 2008). The ischemic heart therefore hosts a vicious cycle in which ischemia begets ischemia by activating I\textsubscript{Na,Late} and by causing diastolic wall tension. Ranolazine interrupts this vicious cycle by inhibiting I\textsubscript{Na,Late} (FIGURE 1).
Ranolazine inhibits $I_{\text{Na,Late}}$ in a concentration-, voltage-, and frequency-dependent manner, and it does so with an $IC_{50}$ value (~6 µM) that compares well with its therapeutic plasma levels (2-6 µM). Ranolazine does not inhibit early peak $I_{\text{Na}}$ ($IC_{50} \geq 300$ µM) but it can marginally inhibit the delayed rectifier $K^+$ current ($I_{\text{Kr}}$) or the late inward $Ca^{2+}$ current ($I_{\text{Late,Ca}^{2+}}$) with $IC_{50}$ values of 12 or 50 µM, respectively (Antzelevitch et al., 2004; Stone, 2008). The net balance of the effects of ranolazine on inward depolarizing currents ($I_{\text{Na,Late}}$, $I_{\text{Late,Ca}^{2+}}$) or outward repolarizing currents ($I_{\text{Kr}}$) translates into modest changes of the action potential duration (approximately 5 to 10 msec prolongation of corrected QT interval (QTc) in patients treated with 1000 mg ranolazine bid) (Scirica et al., 2007). Different Na channel isoforms have been characterized and codenamed Na$_v$.1.1 to Na$_v$.1.8. The majority of studies identified Na$_v$.1.5 as the cardiac channel isoform associated with $I_{\text{Na,Late}}$ (Maltsev and Undrovinas, 2008).

In preclinical models, ranolazine improved diastolic relaxation (“positive lusitropic effect”) in isolated rat hearts exposed to ischemia-reperfusion (Hwang et al., 2009) and in isometrically contracting ventricular muscle strips from end-stage failing human hearts (Sossalla et al., 2008).

**Pharmacologic rationale to probe ranolazine in diastolic dysfunction from antitumor drugs**

In patients with chronic angina, $I_{\text{Na,Late}}$ is activated by hypoxia, accumulation of ischemic metabolites, overproduction of ROS and of reactive nitrogen species (Stone, 2008). In patients treated with anthracyclines, oxygen- and nitrogen-centered reactive species accumulate after redox activation of anthracyclines in cardiomyocytes and endothelial cells (Minotti et al., 2004). By continuously forming ROS, anthracyclines can also diminish oxygen tension and set the stage for cardiac hypoxia and metabolic ischemia (Ganey et al., 1991). 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 (Minotti et al., 2004). Anthracycline-induced diastolic dysfunction should be a good target for drugs, like ranolazine, that inhibited $I_{\text{Na,Late}}$ and prevented cytoplasmic $Ca^{2+}$ overload (FIGURE 2A). It was in keeping with this rationale that ranolazine prevented elevations of LV end diastolic pressure, an index of diastolic dysfunction, in isolated rat heart perfused with doxorubicin$^\dagger$. 

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INa,Late should also be activated by nonanthracycline chemotherapeutics that caused coronary endothelial dysfunction and ischemia, whether silent or heralded by transient arrhythmias. One such mechanism of activation would be potentiated if nonanthracycline chemotherapeutics were combined with anthracyclines that activated INa,Late and caused diastolic dysfunction by their own mechanisms. Ranolazine inhibition of INa,Late might break reciprocal interactions between anthracyclines and nonanthracycline chemotherapeutics in multiagent therapies (FIGURE 2B).

Cardiac benefits from ranolazine would be at the cost of minimal discomfort. Dizziness, nausea, and constipation were seen in patients receiving 1000 or 1500 mg bid in registratory trials (maximum recommended dose is 1000 mg bid in US or 750 mg bid in Europe). Symptoms may be more frequent in patients <60 kg body weight, but dose reductions relieve the side effects of ranolazine without diminishing its efficacy.

Probing ranolazine in diastolic dysfunction from antitumor drugs: bottlenecks and requirements

To focus on diastolic dysfunction from antitumor drugs, and to probe its preventability or curability by ranolazine, one should not recruit patients with pre-existing diastolic dysfunction or any other cardiovascular or metabolic disease that causes or aggravates diastolic dysfunction. The LVEF must be ≥50%, and QTc values must be in the range of normality. In other words, inclusion/exclusion criteria should be tailored to recruit patients who showed “normal” at screening, such that any newly diagnosed diastolic dysfunction could be unambiguously attributed to the effects of antitumor drugs. These requirements introduce a bottleneck in patients’ recruitment, and call for powering the study with a sufficient number of participating centers.

Cardiac function should be measured by techniques that are easy-to-perform in the everyday life of a clinical center and cause little discomfort to cancer patients. Transthoracic echocardiography is a rapid, well-tolerated, noninvasive technique that measures systolic function (LVEF) and diastolic parameters such as the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, and the deceleration time (DT) of early filling velocity. E/A and DT values follow established patterns of alteration in patients with diastolic impaired relaxation or restriction, which can be graded I to III according to deviations from age-adjusted ranges of
normality (Nagueh et al., 2009). Operator bias is minimized by having the same cardiologist perform serial measurements in the same patient. With a due tolerance, E/A ratio and DT can be measured also in patients with a poor acoustic window, as is the case of breast cancer patients carrying expanders or prostheses. Tissue Doppler imaging of early diastolic velocity of mitral annular should be left to operator’s discretion. This technique proved most informative when operators averaged signals acquired at both septal and lateral sides of the mitral annulus (Nagueh et al., 2009); unfortunately, this may not always be feasible in aforesaid patients with a poor acoustic window.

Early diastolic dysfunction may be subtle enough not to be identified by echocardiography. Biomarkers can help to overcome this problem. When the LV wall tension increases, cardiomyocytes release a pre-prohormone B-type natriuretic peptide that is cleaved by circulating endoproteases to release active B-type natriuretic peptide (BNP) and an inactive aminoterminal fragment of the prohormone (Nt-proBNP) (Braunwald, 2008). These peptides are good markers of diastolic altered relaxation or stiffness (Mottram and Marwick, 2005). In oncologic settings, transient post-infusional elevations of BNP or Nt-proBNP might denote fluid overload and LV stretch rather than cardiac dysfunction; at a distance from chemotherapy infusions, however, high BNP or Nt-proBNP would denote authentic cardiotoxicity (Sandri et al., 2005). The circulating half-life of Nt-proBNP is appreciably longer than that of BNP (Braunwald, 2008). Persistent elevations of Nt-proBNP should be easier to capture and to correlate with early diastolic dysfunction even before this could be firmly identified by echocardiography.

Troponin (Tn) measurements provide additional information. In blood samples collected immediately after ending chemotherapy infusions, Tn elevations denote that antitumor drugs caused necrosis of a definite number of cardiomyocytes. This was shown to precede LVEF decreases in some patients, particularly if chemotherapy was high dose and killed more cardiomyocytes than cardiac progenitor cells could replace (Cardinale et al., 2006). At a distance from chemotherapy infusions, however, Tn elevations should more likely denote persistent synergism between subthreshold cellular damage from antitumor drugs and subclinical ischemia from diastolic dysfunction and reduced coronary conductance, with such a synergism causing
some cardiomyocytes to die. Looking at persistent Tn elevations is therefore advisable if one suspected that standard dose chemotherapy was priming the heart to diastolic dysfunction. Regrettably, there is a lack of studies that prospectively assessed elevations of Nt-proBNP and/or Tn in cancer patients at risk for early diastolic dysfunction. Clinical studies of ranolazine should incorporate these laboratory surrogates and make correlations between them and echocardiographic findings.

Further problems may originate from pharmacokinetic interactions between ranolazine and antitumor drugs. Ranolazine is a substrate and weak inhibitor of cytochrome P450 3A enzymes; ranolazine is also a substrate for the drug transporter P-glycoprotein, which is common for drugs that are substrates of cytochrome P450 3A enzymes (Jerling, 2006). Because metabolism and elimination of anthracyclines or nonanthracycline chemotherapeutics also depend on cytochrome P450 3A enzymes and P-glycoprotein (Wilde et al., 2007), concomitant administration of ranolazine could change patient’s exposure to antitumor drugs. Safety reasons therefore advise not to administer ranolazine during chemotherapy. In other words, ranolazine should not be used to prevent diastolic dysfunction; ranolazine should be commenced at the end of chemotherapy to relieve early diastolic dysfunction. In the light of cause-and-effect relations between early diastolic dysfunction and late symptomatic events, this approach still incorporates prevention of delayed cardiotoxicity.

The INTERACT Study

The INTERACT Study (Ranolazine to Treat Early Cardiotoxicity induced by antiTumor drugs, EUDRA-CT 2009-016930-29) was designed at the Drug Sciences and Clinical Pharmacology Center of University Campus Bio-Medico of Rome. INTERACT recruits patients with normal cardiovascular function and no comorbidity, it assesses cardiac function by both echocardiography and measurements of Nt-pro-BNP and TnI, it introduces ranolazine at an early post-chemotherapy assessment if a patient presented with LVEF ≥50% but showed echocardiographic indices of diastolic dysfunction and/or elevations of TnI or Nt-proBNP.

INTERACT was not designed to show that ranolazine could mitigate the lifetime risk of cardiotoxicity. INTERACT was designed as a short term proof-of-concept study that validated the
following hypotheses: i) diastolic dysfunction with preserved LVEF can be detected as early as a patient completed his/her chemotherapy, and ii) ranolazine relieves diastolic dysfunction to the extent that antitumor drugs activated $I_{Na,Late}$ or caused processes that were aggravated by $I_{Na,Late}$.

**Essential study design**

INTERACT is a multicenter Phase IIB open label study that plans to recruit 100 patients, aged 18 to 70 years, scheduled to receive standard dose anthracycline-containing multiagent chemotherapy for the treatment of non-Hodgkin lymphoma or the adjuvant treatment of breast cancer, or standard dose nonanthracycline multiagent chemotherapy for the adjuvant treatment of colorectal cancer. The incidence and curability of cardiotoxicity induced by sequential hits (chemotherapy plus targeted therapy or mediastinal irradiation) is not in the scope of INTERACT. Therefore, INTERACT does not recruit patients who require post-chemotherapy mediastinal irradiation nor recruits breast cancer patients who require post-chemotherapy administration of the anti-epidermal growth factor receptor-2 monoclonal antibody, trastuzumab².

Patients with non Hodgkin lymphoma will receive a cumulative dose of 300 mg of doxorubicin/m². Women with breast cancer will receive 240 mg of doxorubicin/m² or 300 to 600 mg of epirubicin/m², with the latter being equiactive to 200 or 400 mg of doxorubicin/m², respectively. Patients will therefore be exposed to cumulative doses of 200 to 400 mg of doxorubicin equivalents/m², which is equal to or lower than the cumulative dose associated with a 5% risk of systolic dysfunction in patients without risk factors. This should help to identify patients who developed early diastolic dysfunction with preserved LVEF. Recruitment is competitive by center and tumor type. Eleven italian centers participate in INTERACT.

Seven ± three days after completing chemotherapy, patients with echocardiographic indices of diastolic dysfunction, and/or persistent elevations of TnI or Nt-proBNP, are randomized 1:1 to receive ranolazine or most common therapy (i.e., drugs or combination of drugs, like β blockers or others, that the cardiologist feels appropriate according to his/her own experience at his/her own institution). This is the interventional arm of INTERACT. In the light of a preliminary experience at the Coordinating Center, it is expected that ~40% of the recruited patients should enter the interventional arm. Patients randomized to ranolazine or most common therapy are
reassessed at five weeks and then enter a monthly follow-up that ends at six months with a final assessment by both echocardiography and TnI and Nt-proBNP measurements. Patients who show “normal” at an early post-chemotherapy assessment enter an institutional follow-up whose modalities are left to the investigators’ discretion. The institutional follow-up ends at six months with a complete reassessment by both echocardiography and TnI and Nt-proBNP measurements (**FIGURE 3**).

**The objectives of INTERACT**

The interventional arm of INTERACT is designed to meet the following objectives: efficacy with which five weeks ranolazine relieves echocardiographic and/or biohumoral indices of chemotherapy-induced diastolic dysfunction (primary efficacy endpoint), tolerability of five weeks ranolazine in post-chemotherapy cancer patients (primary safety endpoint), tolerability of six months ranolazine (secondary safety endpoint), tolerability of five weeks to six months ranolazine in comparison with most common therapy (exploratory safety endpoint).

The observational arm of INTERACT aims at approximating the incidence of echocardiographic and/or biohumoral indices of diastolic dysfunction in patients who had proven “normal” at an earlier post-chemotherapy assessment. The objectives of this arm are to retrieve information that could prove useful in forthcoming clinical studies. Should a significant incidence of diastolic dysfunction occur in the observational arm, one might consider starting ranolazine in any patient who completed antitumor chemotherapies.

**Post hoc research considerations**

Patients’ accrual started in December 2010. At the time when this Perspective was submitted, 84 patients had been successfully screened and maintained in the study, which corresponds to a net accrual rate of approximately 5 patients/month in the face of the participation of 11 clinical centers. Although study progression was slowed down by unavoidable delays in the involving of participating centers and by patients’ drop out due to tumor-related clinical events, these low figures confirm that INTERACT had to go through the bottleneck of very rigorous inclusion/exclusion criteria. With that said, the bottleneck was worth of all such effort. After INTERACT had been designed or the first patient had been recruited in it, several research papers
appeared and denoted possible confounding factors in the interpretation of ranolazine effects. In pressure overloaded rats, $I_{Na,\text{Late}}$ increases correlated with the expression of neuronal isoforms Na$_v$1.1 and Na$_v$1.6 rather than of Na$_v$1.5 (Xi et al., 2009). In oxidative stress-prone deoxycorticosterone acetate-salt hypertensive mice, which in principle should express a hyperactive $I_{Na,\text{Late}}$, ranolazine relieved diastolic dysfunction by modulating Ca$^{2+}$ effects on the contractile apparatus rather than by inhibiting $I_{Na,\text{Late}}$ (Lovelock et al., 2012). In established models of mechanosensitivity, ranolazine bound to Na$_v$1.5 by utilizing sites other than the canonical F1760 (Beyder et al., 2012). Each of these reports alludes to alternative modes of action of ranolazine in patients with comorbidities. Probing ranolazine in cancer patients without comorbidities may therefore be rewarding to the extent it allows for detecting and treating diastolic dysfunction under the cleanest possible conditions, i.e., when diastolic dysfunction built on chemotherapy activation of $I_{Na,\text{Late}}$ and ranolazine relieved diastolic dysfunction by binding to its known sites in Na$_v$1.5. Once ranolazine efficacy was defined in such settings, clinical studies of more complex patients would be easier to design and to interpret. The experience gained through INTERACT may also help to design studies of the effects of ranolazine on other echocardiographic indices of subclinical cardiotoxicity, like e.g., decreases of myocardial strain (Sawaya et al. 2012). Normal ranges of global or segmental strain, and applicability of reference values to different operational procedures, were defined when INTERACT had already been designed (Dalen et al., 2010; Marwick et al., 2009).

Previous studies suggested that ranolazine could be used to treat diastolic dysfunction. Ranolazine improved diastolic function in patients with previous transmural MI (Hayashida et al., 1994), or in patients with long QT syndrome 3 due to SCN5A gene mutations and slow inactivation of $I_{Na,\text{Late}}$ (Moss et al., 2008); however, these were limited studies of the effects of acute intravenous ranolazine. At the dosages approved in US (500 mg bid for a week and 1000 mg bid in maintenance therapy), oral ranolazine improved echocardiographic indices of myocardial performance in patients with stable angina. This latter study did not focus primarily on diastolic dysfunction and did not assess ranolazine effects at pre-specified checkpoints that could tell how quickly and effectively oral ranolazine exerted and maintained its effects; in fact, patients were
assessed anytime from 30 to over than 200 days after ranolazine was commenced (Figueredo et al., 2011). INTERACT is entirely focused on diastolic dysfunction, titrates oral ranolazine through the dosages approved in EU (375 mg bid for two weeks, followed by 500 mg bid for 10 days and 750 mg bid until the end of the study), and sets its primary and secondary endpoints at prespecified times that should tell more about how quickly and persistently ranolazine exerted its effects.

**Conclusions and perspectives**

Neither oncology nor cardiology would embrace the rationale of INTERACT. In everyday clinical practice both oncologists and cardiologists tend to underestimate the importance of early diastolic dysfunction as a culprit of the lifetime risk of HF or ischemic disease. Cardiovascular assessment of cancer patients remains almost invariably bound to measuring LVEF. INTERACT is a good example of how pharmacology can work for cardio-oncology in improving cardiac surveillance and management of patients exposed to cardiotoxic chemotherapeutics. INTERACT combines appreciation of the mode of action of ranolazine with the need for intercepting and treating early diastolic dysfunction before it slowly progressed toward late sequelae.

Results from INTERACT will pave the road to further studies of ranolazine in cancer patients, which is a steadily growing population at risk for cardiotoxicity. INTERACT should also help to define the working philosophy of cardio-oncology teams and to dignify the role of pharmacologists in such teams.
AUTHORSHIP CONTRIBUTION

G.M. designed INTERACT, served as Study Coordinator, and wrote this Perspective
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FOOTNOTES

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1Belardinelli L. (2010) personal communication

2Radiotherapy for left-sided breast cancer has become much safer than it was in the past; therefore, women scheduled to receive post-chemotherapy radiation to the left chest wall or breast are not considered at risk for multiple hits and can be recruited into INTERACT.
LEGENDS FOR FIGURES

Figure 1  Ranolazine-inhibitable $I_{Na,Late}$ and its role in diastolic dysfunction and ischemia
In the ischemic myocardium, delayed and/or incomplete inactivation of $I_{Na,Late}$ causes elevated intracellular Na$^+$ that exchanges with extracellular Ca$^{2+}$ via the reverse mode Na$^+$-Ca$^{2+}$ exchanger. Excess Ca$^{2+}$ entry causes diastolic wall tension, and the latter causes ischemia that perpetuates $I_{Na,Late}$ activation. By inhibiting $I_{Na,Late}$, ranolazine interrupts the vicious cycle between ischemia and diastolic dysfunction.
NaCh, Na$^+$ channel; NCX, Na$^+$-Ca$^{2+}$ exchanger.

Figure 2  Chemotherapy-induced diastolic dysfunction and the role of ranolazine-inhibitable $I_{Na,Late}$
Panel A: Anthracyclines induce multiple mechanisms of diastolic dysfunction, possibly mediated or amplified by ranolazine-inhibitable $I_{Na,Late}$. ROS, reactive oxygen species; RNS, reactive nitrogen species.
Panel B: Ranolazine inhibition of $I_{Na,Late}$ mitigates diastolic dysfunction induced by vicious cycles between anthracyclines and nonanthracycline chemotherapeutics.

Figure 3  Essential flowchart of the INTERACT study
Figure 1
Figure 2
One week post-chemotherapy assessment

Diastolic dysfunction at echocardiography and/or Nt-proBNP and/or TnI elevations

Ranolazine
Most common therapy

Exclude pre-existing diastolic dysfunction, LVEF <50%, cardiovascular and/or metabolic comorbidity, altered TnI and/or Nt-proBNP, post-chemotherapy targeted therapy or mediastinal irradiation

No abnormality

Institutional follow-up

6 months reassessment (exploratory endpoint)

5 weeks reassessment by echocardiography, Nt-proBNP, TnI

Monthly follow-up

6 months reassessment (secondary endpoint)

Figure 3