Pharmacology of Ranolazine versus Common Cardiovascular Drugs in Patients with Early Diastolic Dysfunction Induced by Anthracyclines or Nonanthracycline Chemotherapeutics: A Phase 2b Minitrial

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ABSTRACT

We have reported that anthracyclines and nonanthracycline chemotherapeutics caused diastolic dysfunction in cancer patients without cardiovascular risk factors. Diastolic dysfunction occurred as early as 1 week after the last chemotherapy cycle and manifested as impaired myocardial relaxation at echocardiography or persistent elevations of B-type natriuretic peptide (BNP) or troponin. The antianginal drug ranolazine shows cardiac relaxant effects that we considered of value to treat early diastolic dysfunction induced by cancer drugs; therefore, 24 low-risk patients with post-chemotherapy diastolic dysfunction were randomized (1:1) to ranolazine or the investigator's choice of common cardiovascular drugs, such as β-blockers and/or angiotensin-converting enzyme inhibitors or loop diuretics (best standard therapy, BST). After 5 weeks, 12 of 12 patients on ranolazine recovered from diastolic dysfunction, whereas 3 of 12 patients on BST did not improve; however, adverse events (not serious) were apparently more frequent for ranolazine than for BST (4/12 vs. 1/12). Ranolazine did not lower blood pressure, whereas BST reduced systolic pressure and caused a trend toward a reduced diastolic pressure. Most patients at randomization showed tachycardia resulting from chemotherapy-related anemia. Hemoglobin recovery contributed to normalizing heart rate in these patients; however, some patients in the ranolazine arm developed tachycardia through chronotropic effects of high BNP levels and returned to a normal heart rate through the effects of ranolazine on decreasing BNP levels. This minitrial describes the potential effects of ranolazine on relieving chemotherapy-related diastolic dysfunction; however, clinical implications of these findings need to be characterized by studies with an adequate sample size.

SIGNIFICANCE STATEMENT

The antianginal drug ranolazine causes cardiac relaxant effects that might relieve diastolic dysfunction. In a clinical pharmacology study, 24 patients were randomized (1:1) to receive ranolazine or common cardiovascular drugs to treat early diastolic dysfunction induced by anthracycline-based or nonanthracycline chemotherapy. Ranolazine relieved diastolic dysfunction in these patients. The safety profile of ranolazine in cancer patients is similar to that of the general population. Compared with common cardiovascular drugs, ranolazine relieved diastolic dysfunction without lowering blood pressure. The sample size of this study was nonetheless too small to permit considerations about the potential clinical value of ranolazine for oncologic patients with early diastolic dysfunction induced by anthracyclines or nonanthracycline chemotherapeutics. This information should be obtained by studies with an adequate sample size.

Introduction

Many cancer drugs can cause cardiotoxicity. Doxorubicin and other anthracyclines inflict multifactorial damage to cardiomyocytes, whereas nonanthracycline chemotherapeutics (e.g., alkylators, antimetabolites, tubuline-active agents) act primarily, but not exclusively, by inducing microvascular dysfunction (Menna et al., 2008). Dose reductions have limited

ABBREVIATIONS: ACEI, angiotensin-converting enzyme inhibitor; AE, adverse event; BMI, body mass index; BNP, B-type natriuretic peptide; BST, best standard therapy; cTnI, cardiac troponin isoform I; DBP, diastolic blood pressure; DT, mean deceleration time of early filling velocity; E/A, mean ratio of peak early filling (E wave) to late diastolic filling (A wave); Hb, hemoglobin; HR, heart rate; late I_{Na}, late inward sodium current; LVEF, left ventricular ejection fraction; Nt-proBNP, aminoterminal fragment of B-type natriuretic peptide prohormone; QTc, heart-corrected QT interval; SBP, systolic blood pressure; ULN, upper limit of normal.

the incidence of cardiac events during the course of chemotherapy; however, heart failure, and/or ischemic disease may occur long after cancer patients have been treated by chemotherapy (Carver et al., 2007; Armenian et al., 2017).

In patients treated by anthracycline-based or nonanthracycline chemotherapies, mild diastolic dysfunction (grade 1, impaired relaxation) was detected at 4 or 12 months; follow-up, often before systolic dysfunction occurred (Altena et al., 2009; Serrano et al., 2015; Klein et al., 2019). In long-term cancer survivors, cardiac events such as heart failure or myocardial infarction were preceded or accompanied by worsening of diastolic dysfunction (grade 2–3, pseudonormal-restrictive patterns) (Armstrong et al., 2015). These notions describe cardiotoxicity as a continuum that begins with mild diastolic dysfunction and then progresses toward more serious events.

Cause-and-effect relations between cancer drugs and diastolic dysfunction should nonetheless be disentangled from risk factors that predispose to diastolic dysfunction (e.g., hypertension, diabetes, overweight) (Borlaug and Paulus, 2011). Recently, we conducted a pilot study of the incidence of diastolic dysfunction in comorbid-free cancer patients treated by anthracycline-based or nonanthracycline chemotherapy. We observed that asymptomatic diastolic dysfunction occurred in 36% of such low-risk patients and could be detected at 1 week after the last chemotherapy cycle. Of note, all patients showed a normal systolic function, as evidenced by a preserved left ventricular ejection fraction (LVEF) (Calabrese et al., 2018). These findings highlight diastolic dysfunction as a very early manifestation of cardiotoxicity, regardless of the influence of competing risk factors.

Diastolic dysfunction was detected as impaired relaxation at echocardiography, but it also occurred in the form of high circulating levels of B-type natriuretic peptide (BNP) (Calabrese et al., 2018). We in fact demonstrated that high BNP levels caused cardiac relaxant effects (*positive lusitropic effects*) that compensated for impaired relaxation before this could be detected by echocardiography. High BNP levels and impaired relaxation were therefore characterized as mutually exclusive manifestations of diastolic dysfunction (Menna et al., 2018a). BNP lusitropy develops through the activation of receptor-coupled guanylyl cyclase, followed by cGMP formation and beneficial effects of protein kinase G on reducing myofilament tension in diastole (Bishu et al., 2011).

Diastolic dysfunction also occurred in the form of increased circulating levels of troponin, a marker of cardiomyocyte necrosis. We suggested that impaired relaxation, by causing energy dissipation in diastole, could synergize with an otherwise reversible damage induced by anthracyclines, eventually causing some cardiomyocytes to die. Accordingly, BNP mitigation of impaired relaxation was shown to diminish cardiac troponin release (Menna et al., 2018b).

Common cardiovascular drugs, like β-blockers or inhibitors of the renin-angiotensin system, cannot be considered specific curative agents of diastolic dysfunction (Paulus and van Ballegoij, 2010). On the other hand, the possible cause-and-effect relations between early diastolic dysfunction and late cardiac sequelae of cancer treatment call for studies that characterize drugs of potential value to treat asymptomatic diastolic dysfunction before it progresses toward more serious cardiac events. The orally available piperazine (ranolazine) might be considered as a valuable option in these settings.

Ranolazine was approved by the US Food and Drug Administration as a first-line or top-on-therapy agent to treat chronic angina. In Europe, ranolazine was approved for the treatment of chronic angina in patients who are inadequately controlled by, or intolerant to, other antianginal drugs. Unlike most common cardiovascular drugs, ranolazine lacks significant hemodynamic effects. Ranolazine acts through lusitropic effects that reduce myocardial interstitial pressure and eventually improve coronary conductance (Stone, 2008). Such effects depend on ranolazine inhibiting the late inward sodium current (late I_{Na}). If persistently activated, as is in the repolarizing ischemic myocardium, late I_{Na} causes inward Na^+ fluxes that force the Na^+-Ca^{2+} exchanger to work in a reverse manner to extrude Na^+. Calcium entry then occurs, activating myofilaments and causing diastolic wall tension (Stone, 2008). Ranolazine inhibition of late I_{Na} therefore relieves diastolic tension.

We considered that also cancer drugs could activate late I_{Na} through, for example, metabolic hypoxia resilting from continued oxyradical formation by anthracyclines or subclinical ischemia resulting from microvascular dysfunction induced by nonanthracycline chemotherapeutics (Minotti, 2013). This offered a rationale to probe ranolazine in patients with an early diastolic dysfunction induced by cancer drugs.

Here we present the results of the INTERACT (ranolazINe to Treat EaRly cArdiotoxiCity induced by antiTumor drugs), a phase 2b study that compared single-agent ranolazine with common cardiovascular drugs to treat early diastolic dysfunction induced by cancer drugs.

Experimental Procedures

Study Design

INTERACT was an open-label, multicenter, real-life phase 2b study. We recruited patients from our previous pilot, prospective, multicenter real-life study in which we evaluated the incidence of diastolic dysfunction 1 week after the end of chemotherapy. The pilot study population comprised 80 evaluable comorbid-free patients, aged 18–70 years and exposed to anthracycline-based adjuvant treatment of breast cancer, anthracycline-based frontline treatment of non-Hodgkin lymphoma, or fluoropyrimidine-/platinum-based adjuvant treatment of colorectal cancer. Before chemotherapy (T0), all patients showed normal diastolic function, an LVEF >50%, and BNP and troponin levels below the upper limit of normal (ULN). One week after the last chemotherapy cycle (T1), all patients showed an LVEF >50%, but 29 patients showed diastolic dysfunction as defined by echocardiographic or biomarker abnormalities (Calabrese et al., 2018). Twenty-four of 29 patients were available for recruitment in INTERACT and were randomized (1:1) to ranolazine or investigator's choice of common cardiovascular drugs (best standard therapy, BST). Randomization was operated centrally by SAS software (SAS Institute, Cary, NC). Efficacy, safety, and cardiovascular pharmacology endpoints were evaluated 5 weeks after randomization (T5) (Fig. 1).

The pilot study and INTERACT were designed to elucidate only the incidence and pharmacologic treatability of diastolic dysfunction induced by frontline chemotherapy. Patients who were candidates for sequential treatment with other potentially cardiotoxic drugs, like the anti epidermal growth factor receptor 2 antibody (trastuzumab) were excluded from the pilot study. Likewise, no patient received mediastinal irradiation or began left-thorax irradiation during the 5-week treatment with ranolazine or BST.

The pilot study and INTERACT conformed with the principles outlined in the Declaration of Helsinki and were approved by the
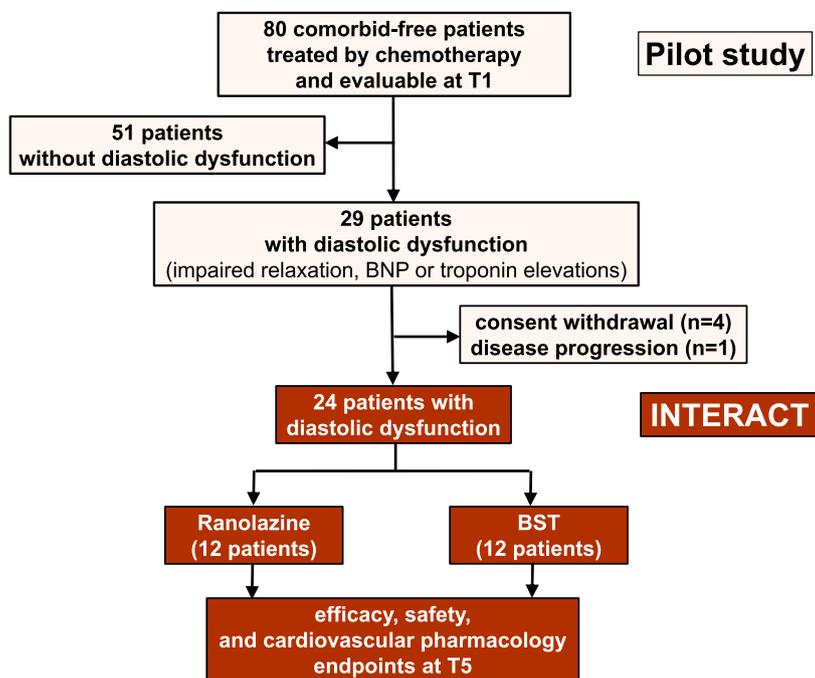
Fig. 1. Flowchart of pilot study and INTERACT from T1 to T5. T1, 1 week after chemotherapy; T5, 5 weeks after randomization.

institutional review board of each participating center. Written informed consent was obtained from all patients.

Patient Characteristics

Patients recruited in INTERACT (*cases*) showed the same demographic, oncologic, and cardiovascular characteristics as those of patients without diastolic dysfunction at the end of the pilot study (*controls*). Cases and controls were balanced for gender and distribution in age groups (<40, 40–60, >60 years) for which ranges of normality of diastolic function at echocardiography were characterized (Nagueh et al., 2009); moreover, the two groups were balanced for oncologic disease, chemotherapy type, and cumulative exposure to

anthracyclines (Table 1). Cases and controls were balanced for systolic blood pressure (SBP) and diastolic blood pressure (DBP), which were normal at T0 and T1; moreover, the two groups were balanced for body mass index (BMI), which averaged well below the value of 29.6 kg/m^2 associated with diastolic dysfunction at 9–12 months after anthracycline-based chemotherapy (Serrano et al., 2015). Cases and controls were balanced for heart rate (HR) at T0 and T1; at the latter time point, however, both groups had a significantly increased HR (Table 2). Cases and controls were balanced for LVEF at T0 but not at T1, with cases showing a marginal but significant lower LVEF compared with controls at T1. Both cases and controls nonetheless showed an LVEF that was ≥10% points higher than the predefined cutoff of preserved LVEF (≥50% points); moreover, longitudinal analyses showed that cases did not develop a net decrement of LVEF from T0 to T1 (see Table 2). Thus, cases were fully representative of the source population of the pilot study and developed diastolic dysfunction with a preserved LVEF per protocol definition.

Study Procedures

Echocardiography. Impaired relaxation was detected by abnormalities of transmitral flow indices at two-dimensiional echocardiography and was defined as borderline or low-for-age ratio of peak early filling (E-wave) to late diastolic filling (A-wave) (E/A ratio), and concomitant borderline or long-for-age deceleration time of early filling velocity (DT). The following age-adjusted ranges of normality were adopted: 1) 0.73–2.33 (20–40 years), 0.78–1.78 (40–60 years), and 0.6–1.32 (>60 years) for E/A ratio; and 2), 138–194 milliseconds (20–40 years), 143–219 milliseconds (40–60 years), and 142–258 milliseconds (>60 years) for DT (Nagueh et al., 2009). Absolute E/A and DT values were then expressed as percentages of normal to permit comparisons between patients of different ages. This was done by the formula in eq. 1:

$$E/A(\text{or } DT) = 100 \times [(\text{absolute value-lower limit of range})]/\text{range} \quad (1)$$

LVEF was calculated by the modified biplane Simpson's rule (Calabrese et al., 2018).

Biomarkers. BNP was measured by the circulating levels of the long lived aminoterminal fragment of its prohormone (Nt-proBNP).

TABLE 1
Demographic and oncologic characteristics of controls and cases
Data are medians with interquartile ranges or percentages. Differences were analyzed by two-tailed Mann-Whitney test, Fisher exact test, or two-tailed χ^2 test, as appropriate.

Characteristics	Controls (n = 51)	Cases (n = 24)	P Value
Age (n, %)			0.090
<40 yr	9 (18%)	2 (8%)	
40–60 yr	36 (70%)	18 (75%)	
>60 yr	6 (12%)	4 (17%)	
Gender			0.480
Male	9 (18%)	3 (13%)	
Female	42 (82%)	21 (87%)	
Oncologic disease			0.480
Breast cancer	35 (69%)	16 (67%)	
Non Hodgkin lymphoma	10 (20%)	6 (25%)	
Colorectal cancer	6 (11%)	2 (8%)	
Chemotherapy			0.844
Anthracycline-based[a,b]	45 (88%)	22 (92%)	
Nonanthracycline[c]	6 (12%)	2 (8%)	
Anthracycline dose (mg/m^2)[d]	240 (240–267)	240 (240–291)	0.844

[a]For breast cancer: doxorubicin (or epirubicin)-cyclophosphamide followed by a taxane, or epirubicin-cyclophosphamide-taxane, or fluorouracil-epirubicin-cyclophosphamide with or without a subsequent taxane.
[b]For non-Hodgkin lymphoma: rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone.
[c]For colorectal cancer: fluorouracil-folinate-oxaliplatinum, or capecitabine-oxaliplatinum.
[d]Expressed as doxorubicin myelotoxic equivalents.

TABLE 2

Cardiovascular characteristics of controls and cases

Data are medians with interquartile ranges. Differences were analyzed by two-tailed Mann-Whitney test or Wilcoxon signed rank test, as appropriate.

Characteristics	Controls ($n = 51$)	Cases ($n = 24$)	P Value
LVEF (%)			
T0	61 (60–65)	60 (60–65)	0.276
T1	62 (60–65)*	60 (58–62)**	0.005
Heart rate (bpm)			
T0	76 (70–81)	78 (70–85)	0.815
T1	83 (75–99)†	85 (77–87)††	0.666
Systolic BP (mm Hg)			
T0	120 (120–130)	120 (110–124)	0.233
T1	120 (115–130)	120 (110–128)	0.446
Diastolic BP (mm Hg)			
T0	80 (70–80)	80 (70–80)	0.766
T1	80 (70–84)	80 (70–80)	0.855
BMI (kg/m^2)			
T0	24 (22–25)	23 (20–25)	0.297
T1	25 (22–28)	23 (19–27)	0.100

*$P = 0.820$ and **$P = 0.170$ for T1 vs. T0.
†$P < 0.001$ and ††$P < 0.01$ for T1 vs. T0.

Troponin was measured by the circulating levels of its cardiac-specific isoform I (cTnI). Both Nt-proBNP and cTnI were measured in heparin-litium plasma by Siemens immuno-chemiluminescence assays for Dimension Vista System (Siemens Healthcare GmbH, Erlangen, Germany) luminescent oxygen channeling immunoassay technology). All assays were centralized at the Clinical Pharmacology Unit of University Campus Bio-Medico of Rome. For patients 18–70 years of age, BNP ULN was set at 125 pg/ml (Siemens Dimension Vista®, 2012). For cTnI, the manufacturer-recommended ULN was rounded from 0.045 to 0.05 ng/ml (Calabrese et al., 2018). Further details have been given elsewhere (Menna et al., 2018a,b).

Study Treatments. Given that the optimal dosage of ranolazine to treat diastolic dysfunction from cancer drugs was unknown, ranolazine was titrated from 375 to 750 mg twice daily as recommended by the European Medicines Agency for the treatment of chronic angina (European Medicines Agency, 2016). Ranolazine was started at the dose of 375 mg twice daily for 2 weeks, followed by up-titration to 500 mg twice daily for 10 days and 750 mg twice daily for 10 additional days. For patients randomized to BST, angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers were the main investigators' choices. BST dosage was left at the investigator's discretion (Table 3). Dose reductions were allowed anytime for patients with signs or symptoms of intolerance to ranolazine or BST.

Study Endpoints

Efficacy. Ranolazine or BST efficacy was defined by the number of patients showing normalization or improvement of impaired relaxation or biomarker elevations. This was a descriptive endpoint; superiority analysis was not in the scope of this study. *Normalization* denoted that echocardiographic indices of relaxation or biomarkers

TABLE 3

Investigator's choice of best standard therapy

Class	Drug(s)	Dosage (mg/day)
ACEI ($n = 5$)	Ramipril	1.25 ($n = 1$) 2.5 ($n = 4$)
β-blocker ($n = 2$)	Bisoprolol	1.25
ACEI + β blocker ($n = 2$)	Ramipril-carvedilol	1.25 + 6.25
	Ramipril-bisoprolol	5 + 2.5
ARB ($n = 1$)	Valsartan	80 mg
ACEI + β-blocker + loop diuretic ($n = 1$)	Ramipril-bisoprolol-furosemide	5 + 1.25 + 25^a
Loop diuretic ($n = 1$)	Furosemide	25

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
^{a}Once every 2 days.

had returned to the ranges of normality; *improvement* denoted that deviations from the range of normality decreased to an extent that the investigators deemed clinically significant. *Treatment failure* was defined as the lack of any improvement or by abnormalities that were not detected at T1 but occurred at T5.

Safety. Safety was defined by the number of patients showing treatment emergent adverse events (AEs). Event severity was graded according to Common Terminology Criteria for Adverse Events, version 5.0 (U.S. Department of Health and Human Services, 2017).

Cardiovascular Pharmacology Endpoints. These endpoints were defined as any effect that ranolazine or BST caused on cardiovascular parameters other than myocardial relaxation or biomarkers.

Other Conditions

HR was determined by 12-lead ECG. Where indicated, changes in HR from T0 to T1 and from T1 to T5 were normalized to concomitant changes of hemoglobin (Hb). Δbpm/ΔHb ratios were then compared with a range of *normality*, defined as the interquartile range for Δbpm/ΔHb ratios of all 24 cases. Rate-corrected QT interval (QTc) was calculated by the Bazett formula (Yap and Camm, 2003). Doxorubicin myelotoxic equivalents were calculated by assuming an epirubicin:doxorubicin conversion factor of 0.66 (Ewer, 2013). Data were expressed as medians with interquartile ranges or absolute number and percentages. Data from a same arm were compared by two-tailed Wilcoxon Signed Rank test or one-way repeated-measures analysis of variance with Bonferroni's post hoc test, as appropriate. Data from different arms were compared by two-tailed Mann-Whitney test or one-way Kruskall-Wallis analysis of variance with Dunn's post hoc test, as appropriate. Categorical variables were analyzed by χ^2 test or Fisher's exact test. Differences were considered significant when the P value was <0.05.

Results

Efficacy Endpoint. INTERACT recruited and randomized 24 patients, showing a total 26 protocol-defined indices of diastolic dysfunction (impaired relaxation, $n = 11$; BNP > ULN $n = 12$; cTnI > ULN $n = 3$). No patient presented with impaired relaxation and a concomitant BNP > ULN (Table 4). Impaired relaxation and biomarker levels were normalized or improved in all patients randomized to ranolazine. In the BST arm, two patients with impaired relaxation did not improve, whereas a third patient showed normalization of impaired relaxation but developed BNP levels > ULN at T5. Thus, the BST arm had three treatment failures versus none in the ranolazine arm (see also Table 4). Treatment failures occurred in patients randomized to β-blocker and/or ACEI. Patterns of treatment efficacy or failure are shown in Fig. 2.

Safety Endpoint. Adverse events of mild to severe intensity occurred in 4 of 12 patients randomized to ranolazine and in 1 of 12 patients randomized to BST (Table 5). All AEs were judged as not serious (i.e., they did not result in any of the life-threatening or disabling outcomes that US Food and Drug Administration identified for defining the seriousness of AEs) (U.S. Department of Health and Human Services, 2012). All AEs were judged as certainly or probably related to study treatment. For one patient with ranolazine-related constipation and tinnitus, uptitration from 375 to 500 mg of ranolazine bid was stopped and the patient was maintained on 375 mg bid until evaluation at T5. In BST arm, one patient complained about asthenia induced by the ACEI, ramipril, which was managed by reducing ramipril from 2.5 to 1.25 mg/day Dose reductions did not interfere

TABLE 4
Efficacy of 5 weeks of ranolazine or best standard therapy (BST) on chemotherapy-induced diastolic dysfunction

Arm	Event at T1	Event Outcome at T5	Postrandomization Events	Treatment Failures
Ranolazine ($n = 12$)	Impaired relaxation ($n = 5$)	Normalized	None	None
	Impaired relaxation + cTnI > ULN	Normalized/normalized	None	
	cTnI > ULN	Normalized	None	
	BNP > ULN ($n = 4$)	Normalized ($n = 3$), Improved ($n = 1$)	None	
	BNP > ULN + cTnI > ULN	Improved-normalized	None	
BST ($n = 12$)	Impaired relaxation ($n = 2$)	Normalized	None	3
	Impaired relaxation[a]	Normalized	BNP > ULN[a]	
	Impaired relaxation[b]	Failure	None	
	Impaired relaxation[c]	Failure	None	
	BNP > ULN ($n = 7$)	Normalized ($n = 4$), Improved ($n = 3$)	None	

BNP, B-type natriuretic peptide; cTnI, cardiac troponin isoform I; T1, 1 week after chemotherapy; T5, 5 weeks after randomization; ULN, upper limit of normal.
[a]Patient treated by ramipril (2.5 mg/day).
[b]Patient treated by bisoprolol (1.25 mg/day).
[c]Patient treated by bisoprolol + ramipril (2.5 mg/day + 5 mg/day).

with normalization or improvement of diastolic dysfunction by ranolazine or BST (see also Table 5).

Cardiovascular Pharmacology Endpoints. Neither ranolazine nor BST caused effects on LVEF or BMI, which remained unchanged both between and within arms. Previous studies showed that ranolazine caused a modest prolongation of QTc, probably reflecting a moderate inhibition of delayed rectifier K^+ current (Antzelevitch et al., 2004). Here, 5 weeks of ranolazine did not prolong QTc in cancer patients. Moreover, ranolazine and BST arms were balanced for QTc at T1 and T5, and no patient presented at T5 with QTc values higher than gender-related pathologic thresholds (450 milliseconds for men, 470 milliseconds for women) (Table 6).

BST, but not ranolazine, caused a significantly reduced SBP, which was also borderline lower compared with ranolazine arm; moreover, BST caused an insignificant decrease in DBP ($P = 0.160$) (see also Table 6). Individual changes of blood pressure, measured as Δ mm Hg from T1 to T5, were characterized. Cases in the BST arm showed a significant trend toward a lowered SBP compared with cases in the ranolazine arm, but this was not observed when all cases in BST and ranolazine arms were compared for DBP; however, a significant difference occurred when only cases with Δ mm Hg < 0 were considered, as the patients in BST arm showed greater decrements of DBP (Fig. 3). Collectively, data in Fig. 3 and Table 6 showed that BST lowered blood pressure, whereas ranolazine lacked significant effects.

BST and ranolazine arms were balanced for HR at T0, T1, and T5. At the latter time point, all cases showed essentially the same HR they showed at T0. Patients in the ranolazine arm were nonetheless characterized by a trend toward tachycardia at T1. In recovering a normal HR at T5, ranolazine cases therefore lost more beats per minute compared with BST cases (Table 7).

Loss or gain of hemoglobin is known to increase or decrease HR in cancer patients (Menna et al., 2018a). Hemoglobin effects on HR probably occur through a modulation of sympathetic reflexes from carotid body (Lahiri et al., 2006). We therefore normalized individual changes in HR (Δbpm) to concomitant changes of Hb (ΔHb). At T1 and T5, all cases of BST arm showed Δbpm/ΔHb ratios within the range of normality (i.e., they gained or lost bpm in response to Hb decrements at T1 or Hb recovery at T5). In contrast, some cases in the ranolazine arm showed Δbpm/ΔHb ratios outside the range of normality, both at T1 and T5. These patients gained or lost bpm in response to factors other than Hb changes; of note, these patients were randomized to ranolazine because of BNP levels > ULN at T1 (denoted by asterisks in Fig. 4A).

We next characterized how patients randomized to ranolazine or BST compared with respect to the magnitude of BNP increases above ULN at T1 or BNP decrements toward ULN at T5. Both changes were remarkably more evident for cases of ranolazine arm compared with cases in the BST arm (Fig. 4B). For the patient who developed BNP > ULN after an apparent ACEI normalization of impaired relaxation, ΔBNP was of a lower magnitude compared with cases in the ranolazine arm, and Δbpm/ΔHb ratio at T5 was within the
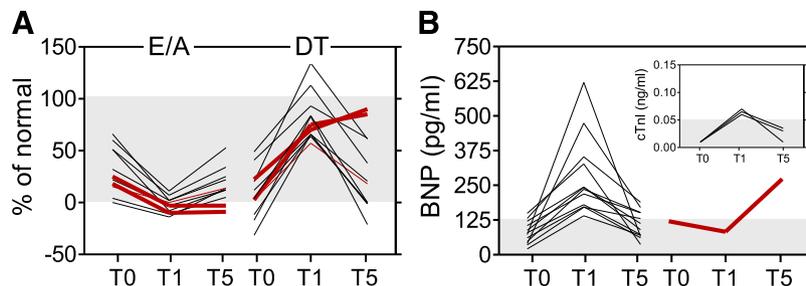

Fig. 2. Patterns of treatment efficacy or failure in patients with impaired relaxation or BNP or cTnI > ULN. For impaired relaxation, treatment efficacy was denoted by normalization of E/A decrements and DT prolongations. For biomarkers, treatment efficacy was denoted by normalization or improvements of BNP or cTnI > ULN. Shaded areas denote ranges of normality. (A) E/A ratio and DT at T0 (baseline), T1 (1 week after chemotherapy), T5 (5 weeks after randomization to ranolazine or BST). Values are expressed as percentages of normal. (B and inset) Changes in BNP and cTnI at T0, T1, and T5. Bold red lines denote patients who did not normalize E/A and DT or developed BNP > ULN after randomization to BST. BNP was measured as Nt-proBNP.

TABLE 5
Ranolazine- or best standard therapy (BST)-related adverse events (AEs) from T1 to T5

Patients with AEs	AE	AE Intensity	AE Seriousness	AE Management	Diastolic Dysfunction Event at T1	Event Outcome at T5
Ranolazie arm (n = 4)	Constipation	Moderate	Not serious	None	BNP > ULN	Normalized
	Constipation	Severe	Not serious	None	BNP > ULN	Normalized
	Nausea	Mild-mild	Not serious	None	Impaired relaxation	Normalized
	Constipation-tinnitus	Severe-moderate	Not serious	Dose reduction[a]	cTnI > ULN	Normalized
BST arm (n = 1)	Asthenia	Severe	Not serious	Dose reduction[b]	BNP > ULN	Improved

AE, adverse event; BNP, B-type natriuretic peptide; BST, best standard therapy; cTnI, cardiac troponin isoform I; T1, 1 week after chemotherapy; T5, 5 weeks after randomization; ULN, upper limit of normal.
[a]From 500 to 375 mg twice daily.
[b]Ramipril reduced from 2.5 to 1.25 mg/day.

range of normality (see also Fig. 3, A and B, columns with arrow).

When examined in aggregate, all cases randomized to BST or ranolazine because of having BNP > ULN at T1 showed Δbpm/ΔHb ratios that correlated with BNP deviations above ULN at T1 or toward ULN at T5; however, separate analyses of the two arms showed that such correlation was contributed only by patients in the ranolazine arm (Fig. 5). Collectively, data in Figs. 4 and 5 suggested that some patients in the ranolazine arm showed HR changes that were influenced by BNP rather than Hb.

Discussion

General Considerations on Ranolazine Efficacy and Safety in Cancer Patients. We probed the lusitropic effects of ranolazine in patients with an early diastolic dysfunction induced by cancer drugs. Ranolazine normalized or improved diastolic dysfunction in each of 12 evaluable patients. Also, BST was effective at relieving diastolic dysfunction, but treatment failure occurred for 3 of 12 patients (see Fig. 2; Table 4).

Treatment emergent AEs were apparently more frequent for patients in the ranolazine arm (see Table 5). Ranolazine

TABLE 6
Cardiovascular parameters in ranolazine or best standard therapy (BST) arms from T1 to T5
Data are medians with interquartile ranges and were analyzed by two-tailed Mann-Whitney test (for comparisons between arms) or two-tailed Wilcoxon signed rank test for comparisons within arms.

Parameters	Ranolazine (n = 12)	BST (n = 12)	P Value
LVEF (%)			
T1	60 (56–61)	60 (59–62)	0.610
T5	60 (58–65)	60 (58–64)	0.837
P (T1 vs. T5)	0.324	0.572	
SBP (mm Hg)			
T1	120 (110–130)	120 (113–120)	0.845
T5	120 (111–129)	110 (110–115)	0.051
P (T1 vs. T5)	0.887	0.046	
DBP (mm Hg)			
T1	78 (70–80)	80 (70–85)	0.613
T5	78 (70–80)	70 (70–79)	0.364
P (T1 vs. T5)	0.665	0.160	
QTc (mm Hg)			
T1	423 (405–430)	405 (390–420)	0.220
T5	419 (400–430)	417 (410–439)	0.772
P (T1 vs T5)	0.689	0.220	
BMI (kg/m^2)			
T1	21 (19–26)	25 (20–27)	0.338
T5	22 (20–26)	25 (20–28)	0.400
P (T1 vs T5)	0.102	0.824	

was titrated, as recommended for patients with chronic angina, but we cannot exclude that this dose was too high to treat an early and asymptomatic manifestation of cardiotoxicity. Accordingly, reducing ranolazine dosage could resolve AEs in one patient without interfering with normalization of diastolic function. On the other hand, we cannot exclude that AEs from common cardiovascular drugs were taken for granted in a real-life study and were therefore underreported by the investigators. Ranolazine AEs, such as constipation and nausea or tinnitus, were nonetheless consistent with the known characteristics of ranolazine (Keating, 2013). Moreover, ranolazine did not prolong QTc. The safety profile of ranolazine in oncologic patients was therefore satisfactory.

Cardiovascular Pharmacology Endpoints. BST, but not ranolazine, reduced SBP; showed a trend toward reducing DBP; and caused asthenia of a severe intensity in one patient (see Fig. 3; Table 6). These findings anticipate potential advantages of ranolazine treatment over common cardiovascular drugs; in fact, medication of early asymptomatic cardiotoxicity is uncommon in real-life oncology, and many doctors refrain from prescribing cardiovascular drugs that could expose cancer patients to hypotension or asthenia (Minotti, 2013).

Cancer patients' compliance to an early medication of cardiotoxicity might also be limited by HR-lowering effects of most common cardiovascular drugs. We have shown that all cases randomized to BST or ranolazine presented at T5 with the same HR they had before starting chemotherapy. The HR-lowering effects of BST could not be distinguished from concomitant HR-lowering effects owing to Hb recovery, which likely served as the major determinant of HR normalization. In contrast, ranolazine seemed to normalize HR through an Hb-independent negative chronotropic effect. Our data show that such an effect was apparent but reflected ranolazine's ability to improve or normalize BNP elevations, which were of a greater magnitude compared with BNP elevations in BST cases. Three lines of evidence support this notion: 1) ranolazine caused Hb-independent HR decrements in patients with BNP > ULN and Hb-independent tachycardia at T1; 2) ranolazine lacked HR-lowering effects in patients with BNP < ULN; and 3) HR changes correlated with BNP levels (see Figs. 4 and 5).

The effects of ranolazine on HR must be reconciled with the multifaceted role BNP may play in cancer patients. In addition to relieving impaired relaxation, BNP elevations can in fact increase HR in a concentration-related manner (Menna et al., 2018a,b), which probably occurs via BNP stimulation of cGMP formation in sinoatrial node, followed
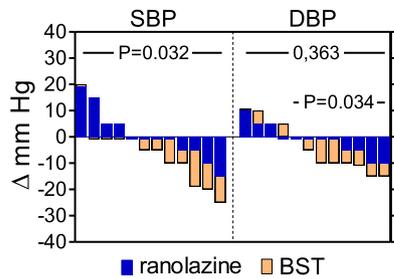
Fig. 3. Individual changes in systolic or diastolic blood pressure after 5 weeks of ranolazine or BST. Individual blood pressure changes were measured as Δ mm Hg from T1 (1 week after chemotherapy) to T5 (5 weeks after randomization to ranolazine or BST). Data were analyzed by two-tailed Mann-Whitney test. Where indicated, differences in DBP changes were analyzed only for ranolazine or BST cases that showed negative Δ mm Hg values.

by activation of L-type Ca^{2+} current and higher conduction velocity within the node and toward the surrounding cardiomyocytes (Springer et al., 2012). Ranolazine, by inducing positive lusitropic effects, relieved the diastolic tension that stimulated BNP elevations and blunted the positive chronotropism induced by high BNP levels.

The lack of an authentic negative chronotropism of ranolazine was consistent with previous findings of preclinical and clinical studies. Ranolazine lacked significant β-blocking and HR-lowering effects in laboratory animals (Zhao et al., 2011) but induced bradycardia only in limited experiments that adopted suprapharmacologic doses of ranolazine (Létienne et al., 2001; Dhalla et al., 2009). Moreover, ranolazine did not significantly lower HR in patients with chronic angina, regardless of whether the patients were also taking β-blockers as part of the anti-ischemic therapy (Rousseau et al., 2005; Stone, 2008).

Study Limitations and Strengths. The main limitation of this study is sample size. The pilot study was designed to recruit 100 patients and to intercept 40 patients with diastolic dysfunction at T1 (Minotti, 2013); however, only 80 patients were evaluable at T1, and only 29 of them showed diastolic dysfunction. The incidence of diastolic dysfunction in the pilot study was in fact congruent with that anticipated by the study protocol (36% vs. 40%), but the number of patients to recruit in INTERACT was significantly reduced. Moreover, only 24 of 29 randomizable patients were eventually assigned to study treatment (see Fig. 1). From T0 to T1 and from T1 to randomization, sample size reduction was primarily due to patients' refusal to participate, consent withdrawal, or failure

TABLE 7
Heart rate in patients of ranolazine or best standard therapy (BST) arms
Data are medians with interquartile ranges and were analyzed by two-tailed Mann-Whitney test for comparisons between arms and by one-way repeated measures analysis of variance with Bonferroni's post hoc test for comparisons within arms.

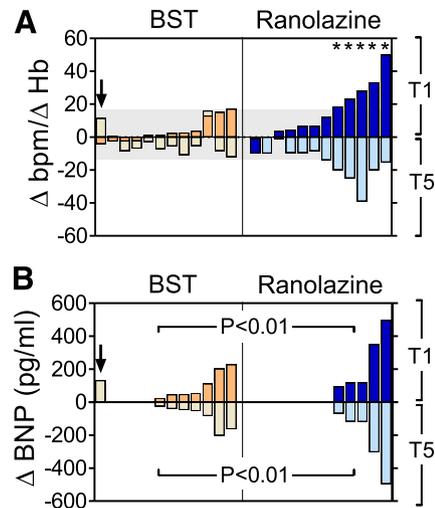|	Ranolazine (n = 12)	BST (n = 12)	P Value
Heart rate (bpm)			
T0	76 (70–80)	78 (70–83)	0.966
T1	95 (79–101)	78 (75–94)	0.088
T5	75 (69–79)	73 (64–80)	0.728
P (T0-T1)	<0.01	>0.05	
P (T1-T5)	<0.01	>0.05	
P (T0-T5)	>0.05	>0.05	

Fig. 4. Hb-adjusted HR and BNP elevations in ranolazine or BST arms (A) shows individual increases or decreases in bpm (Δbpm) at T1 or T5 in ranolazine and BST arms. All values were normalized to concomitant increases or decreases of Hb (ΔHb). The shaded area denotes ranges of normality for Δbpm/ΔHb ratios at T1 or T5, calculated as the interquartile range of Δbpm/ΔHb ratios in the complete cohort of 24 cases at each time point. Columns with asterisks identify cases of ranolazine arm that presented at T1 with BNP > ULN. (B) Net excursions of BNP from ULN at T1 and toward ULN at T5. Differences were calculated by two-tailed unpaired Mann-Whitney test. Arrows denote the patient in BST arm who developed BNP > ULN at T5. BNP was measured as Nt-proBNP, and ΔHb was expressed as grams per deciliter.

to attend study visits. These facts are not uncommon in cardio-oncology trials (Pituskin et al., 2017). They denote that much needs to be done for improving patients' awareness of cardiovascular consequences of cancer treatment.

Further limitations pertain to the role of late I_{Na}. Ranolazine improved diastolic indices in murine models of anthracycline-related cardiomyopathy, but whether this depended on a canonical inhibition of late I_{Na} was not demonstrated (Cappetta et al., 2017). More in general, some reports challenged cause-and-effect relations between late I_{Na} activation, Ca^{2+} overload, and diastolic dysfunction (Papp et al., 2014; Runte et al., 2017). Here it is worth noting that both anthracyclines and nonanthracycline chemotherapeutics might increase diastolic $[Ca^{2+}]_I$ by mechanisms that do not necessitate an activation of late I_{Na} but either stimulate Ca^{2+} release from sarcoplasmic reticulum or inhibit Ca^{2+} reuptake in it (Minotti et al., 2004; Zhang et al., 2010). On a different note, ranolazine may improve diastolic relaxation by mechanisms that do not necessitate an inhibition of late I_{Na} but reduce myofilament sensitivity to Ca^{2+} (Lovelock et al., 2012). Ranolazine could therefore improve diastolic dysfunction even if late I_{Na} was not involved.

Despite limitations and uncertainties, INTERACT shows some important strengths. All patients randomized to study treatment were characterized by impaired relaxation or biomarker abnormalities that either compensated for impaired relaxation (BNP > ULN) or associated with it (cTnI > ULN). No patient presented with LVEF <50% or grade ≥2 diastolic dysfunction. Thus, ranolazine or BST was studied in patients showing a very early manifestation of diastolic dysfunction (Nagueh et al., 2009, 2016), precisely representing the target of pharmacologic interventions aimed at preventing a progression of cardiotoxicity toward more serious sequelae.
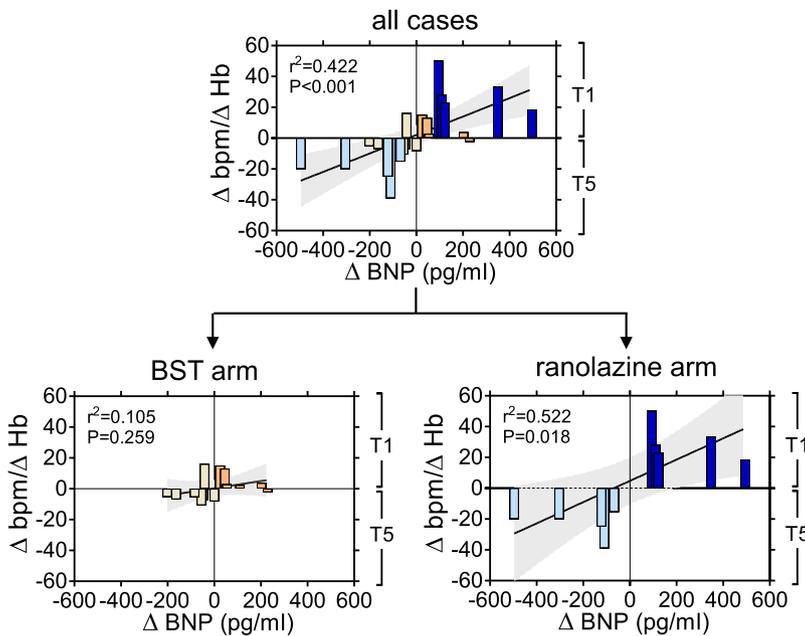
Fig. 5. Correlations between Hb-adjusted changes of heart rate and BNP levels. The upper panel shows the correlation between Δbpm/ΔHb ratios and net excursions of BNP from ULN at T1 or toward ULN at T5 for all cases randomized to study treatments. Lower panels show that Δbpm/ΔHb ratios correlated with BNP excursions for cases of ranolazine arm, but not for cases of BST arm. Shaded areas denote 95% confidence intervals of linear regressions. BNP was measured as Nt-proBNP, and ΔHb was expressed as grams per deciliter.

On a different note, INTERACT confirmed that impaired relaxation and BNP elevations were mutually exclusive manifestations of diastolic dysfunction, not only because no patient presented at T1 with impaired relaxation and a concomitant BNP > ULN but also because one patient in the BST arm responded to an ACEI by switching from impaired relaxation to BNP > ULN. Given that BNP serves as an endogenous lusitropic agent, this limited observation suggests that BNP increased to compensate for a lack of efficacy of the ACEI to relieve impaired relaxation in that patient. We acknowledge that in nononcologic patients, BNP levels actually increased with the severity of diastolic dysfunction at echocardiography, as if BNP lacked lusitropic effects and failed to mitigate diastolic abnormalities (Lubien et al., 2002). We nonetheless observe that ≥50% of such patients presented with risk factors such as hypertension and/or diabetes or coronary artery disease, which probably caused different mechanisms of diastolic dysfunction compared with the action of cancer drugs in comorbid-free patients.

We mentioned that some treatment failures occurred in the BST arm but not in the ranolazine arm. This finding by no means implies that ranolazine was superior to BST. Superiority analyses were not in the scope of INTERACT and would have not been in light of the limited sample size of this study. Treatment failures only denoted that even a mild diastolic dysfunction can be difficult to treat, which in principle would be consistent with the liability of mild dysfunction to progress toward moderate or severe dysfunction. With that said, we noted how effectively 5 weeks of ranolazine relieved diastolic dysfunction in cancer patients, which was reminiscent of the efficacy with which 4 weeks of ranolazine improved myocardial relaxation and perfusion in patients with chronic angina (Venkataraman et al., 2009). Moreover, the efficacy with which ranolazine normalized HR in patients with chronotropic levels of BNP was reminiscent of the higher protective efficacy ranolazine has shown in patients with acute coronary syndrome and increased BNP levels as compared with patients with low BNP levels (Morrow et al., 2010).

Conclusions

We have shown that ranolazine, being a lusitropic agent, is potentially able to relieve early diastolic dysfunction induced by anthracyclines or nonanthracycline chemotherapeutics. The safety profile of ranolazine in oncologic patients seems similar to that characterized for the general population. The sample size of this exploratory study is nonetheless too small to permit considerations about the clinical use of ranolazine for patients with chemotherapy-related diastolic dysfunction. An exploration of potential different mechanisms of action of ranolazine in patients with impaired relaxation or BNP > ULN is also precluded at this time. The efficacy, safety, and pharmacodynamics of ranolazine in oncologic patients with diastolic dysfunction should be characterized by studies with an adequate sample size.

Authorship Contributions

Participated in research design: Minotti.

Conducted experiments: Menna, Calabrese, Greco, Armento, Annibali, Marchesi.

Contributed new reagents or analytic tools: Menna.

Performed data analysis: Minotti, Salvatorelli, Reggiardo.

Wrote or contributed to the writing of the manuscript: Minotti, Menna, Calabrese, Greco, Armento, Annibali, Marchesi, Salvatorelli, Reggiardo.

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