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REVIEW

The emerging issue of cardiac dysfunction induced by antineoplastic angiogenesis inhibitors

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Left ventricular dysfunction from anticancer drugs has emerged as a relevant problem in the clinical and scientific communities. Anthracycline toxicity has always been the most relevant, but with the increasing use of biological targeted therapies in treatment protocols, with an increasing number of cancer survivors, new toxicities have been increasing in more recent years. Cardiomyopathy after ErbB2 inhibitors has been intensively studied. Another important class of biological anticancer drugs are vascular endothelial growth factor (VEGF) inhibitors. VEGF signalling is crucial for vascular growth, but it also has a major impact on myocardial function. Also, it is important to note that such angiogenesis inhibitors are multitargeted in most cases, and can produce a broad spectrum of cardiovascular side effects. Here we review the mechanisms and pathophysiology of the most significant cardiotoxic effects of antiangiogenic drugs, and particular attention is drawn to LV dysfunction, discussing the assessment and management on the basis of the most recent cardio-oncological findings and heart failure guidelines.

Keywords Left ventricular dysfunction • Anti-angiogenic drugs • VEGF • Multitargeted tyrosine kinase inhibitors • Cardiovascular risk factors • Hypertension

Introduction

While survival after cancer has improved, cardiotoxicity due to antineoplastic treatments has emerged as a relevant issue.[1] Potential cardiovascular toxicities linked to anticancer agents include QT prolongation and arrhythmias, myocardial ischaemia and infarction, hypertension and/or thrombo-embolism, LV dysfunction, and heart failure (HF). The latter is variable in severity, may be reversible or irreversible, and can occur soon after or as a delayed consequence of anticancer treatments.[2]

The induction of late-onset HF after anthracyclines[3] has historically been the most relevant problem. However, also biological drugs, 'targeted' to affect specific growth signalling pathways, do not act exclusively on cancer cells. This is particularly true for the heart, especially during stress conditions, for instance when in the presence of hypertension, hypertrophy, previous anthracycline exposure, and in general any factor which can be deleterious *per se* to the myocardium and might exacerbate the cardiotoxicity of such drugs. With regard to cardiotoxic biological anticancer drugs that induce HF, the best known are ErbB2 blockers, i.e. trastuzumab.[4] In addition, biological therapies which interfere with the vascular endothelial growth factor (VEGF) signalling pathway are effectively and widely used in cancer treatment. So far, at least five VEGF targeting agents have been approved by the US Food and Drug Administration (FDA): bevacizumab, sunitinib, sorafenib, pazopanib, and vandetanib.[5] By inhibiting VEGF signalling, these compounds inhibit tumour angiogenesis;[6] but since VEGF is also a fundamental player in the maintenance of cardiovascular homeostasis, not surprisingly, antiangiogenic drugs have been found to be associated with LV systolic dysfunction and HF.

Effects of anticancer drugs with antiangiogenic properties on the cardiovascular system

Antiangiogenic drugs used in anticancer therapies include the following.

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(i) Bevacizumab is a humanized monoclonal antibody directed against VEGF-A that activates signalling in endothelial cells, and is currently approved for the treatment of advanced carcinoma of the lung, breast, and colon–rectum.[7,8] Results from randomized trials suggest that bevacizumab increases the incidence of HF, especially after prior chemotherapy (3%; 1% with bevacizumab alone).[9] In another study concerning metastatic breast cancer, the concomitant use of bevacizumab and paclitaxel (which binds to tubulin and inhibits the disassembly of microtubules, thus inhibiting cell division), did not significantly change the incidence of LV dysfunction compared with paclitaxel alone (0.8% vs. 0.3%).[10] A recent meta-analysis[11] showed that bevacizumab in metastatic breast cancer increases the risk of grade 3 or 4 HF by five-fold, with an overall incidence of 1.6%.

Other FDA-approved agents are small multitargeted kinase inhibitors.

(ii) Sunitinib malate is a multitargeted[6] tyrosine kinase inhibitor (TKI) with strong antiangiogenic activity, widely used in metastatic renal cancer and in imatinib-resistant gastrointestinal stromal tumour (GIST).[1,12] Its targets include many receptors: the VEGF receptors (VEGFR1, -2, and -3), c-Kit, platelet-derived growth factor receptor (PDGFR) α and β, rearranged during transfection (RET), FMS-related tyrosine kinase 3 (FLT3), and colony-stimulating factor 1 receptor (CSF1R). In retrospective series and clinical trials, sunitinib has been associated with a decrease in EF in up to 28% of treated patients, and with clinically overt HF in 3–15% of patients.[13–16]

(iii) The multitargeted TKI sorafenib inhibits VEGFR, PDGFR, c-Kit, and the RAF-1 protein. It induces both tumour apoptosis and disruption of the tumour vasculature.[17] Sorafenib is approved for treatment of patients suffering from renal cancer, as second-line treatment after failure of sunitinib, and for hepatocarcinoma.[18,19] In a pivotal trial, in advanced hepatocellular carcinoma, the incidence of cardiac events was similar between the sorafenib group and the placebo group,[19] but in another observational, single-centred study, 14 out of 25 sorafenib-treated patients had a cardiac event (abnormal cardiac enzymes, symptomatic arrhythmias requiring treatment, new LV systolic dysfunction, acute coronary syndrome). Such cardiac events were associated with increased creatine kinase- MB and cardiac troponin T; 3 of the 14 patients showed abnormal EF at the moment of the event.[20]

(iv) Pazopanib is currently used for treatment of advanced renal cancer; cardiac dysfunction was observed in 4 out of 586 patients.[21]

(v) Vandetanib is used for medullary thyroid cancer: there are known HF events in patients on this drug.[5]

In summary, among the five VEGF targeting agents approved by the US FDA, bevacizumab, a monoclonal antibody directed against VEGF-A, has been reported to induce HF. In contrast to bevacizumab, the other four drugs are TKIs: among them, sunitinib and sorafenib are the best known. They are multitargeted, since they inhibit both tumour angiogenesis (via VEGFR and PDGFR inhibition), and cancer progression, which is mediated by other kinases that also play important roles in other organs, including the cardiovascular system. Inhibition of all these targets produces cardiotoxic effects.[6]

Cardiovascular pathophysiology induced by antiangiogenic anticancer drugs

Angiogenesis plays a fundamental role in tumour progression.[22] In mammals, the VEGF family comprises VEGF-A (commonly referred to as VEGF), VEGF-B, -C, -D, and placental growth factor (PlGF), along with their receptors VEGFR-1, -2, and -3.[23]

VEGF-C and -D have lymphangiogenic and angiogenic activities. They are able to activate primarily VEGFR-3 on endothelial cells in lymphatic vessels and VEGFR-2 on blood vessels.[24]

VEGF-A, secreted by up to 60% of human cancers,[6,25] induces microvascular permeability, formation of new blood vessels, vasodilation, and hypotension when infused intravenously.[23] It binds to VEGFR-1 and -2, activating their kinase function and subsequent downstream signalling cascades that lead to increased capillary permeability, production of nitric oxide (NO), endothelial cell proliferation, and resistance to stresses, facilitating endothelial cell migration and sprout formation, which results in tumour expansion and metastasis.[6]

Along with its role in cancer growth and metastasis, the VEGF pathway is also essential for maintenance of cardiovascular homeostasis. Inactivation of endogenous VEGF with an adenoviral vector encoding a decoy VEGFR led to a net reduction in capillary density, impaired cardiac hypertrophy, and loss of contractile function after pressure overload in mice subjected to transverse aortic constriction (TAC).[26] Microvascular plasticity allows adaptation of the vascular network, and thus oxygen supply to enhanced metabolic demand due to pressure overload. Inhibiting the VEGF pathway blocks such plasticity, contributing to maladaptive hypertrophy of cardiomyocytes (*Figure 1*).[27] In line with this work, Zentilin and

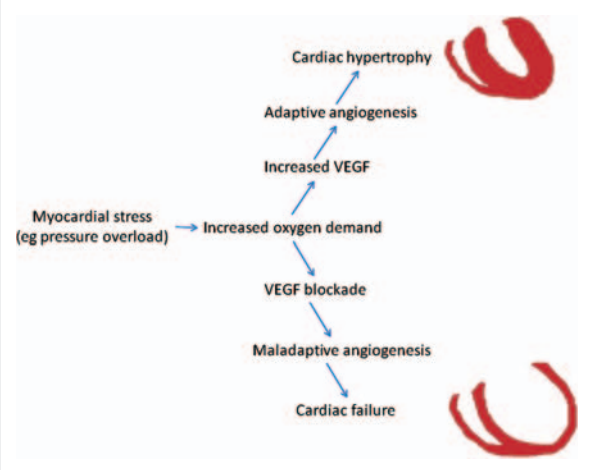

Figure 1 Vascular endothelial growth factor (VEGF) signalling as a link among myocardial demand, microvascular coronary network, and cardiac hypertrophy or failure during myocardial stress. Modified from Lévy.[27]

colleagues[28] showed that expression of VEGF after myocardial infarction (MI) improves contractility, prevents pathological remodelling, and preserves viable cardiac tissue.

Interestingly, Chiusa and colleagues[29] suggested that cancer therapy with anthracyclines modulates VEGF release and its cellular receptors in cardiac microvascular endothelial cells and adult rat ventricular myocytes, therefore altering paracrine signalling in the myocardium.

Placental growth factor binds to VEGFR-1 and its co-receptors Neuropilin-1 and -2, stimulating endothelial growth, migration, and survival, chemoattracts proangiogenic macrophages, and determines the pre-metastatic niche, inducing tumour and stromal cell proliferation and migration.[23] Interestingly, VEGF-B also binds to VEGFR-1 and Neuropilin-1, but, unlike PlGF, its angiogenic activity seems restricted to the ischaemic heart.[23,30] Additionally, PlGF and VEGF-B could provide novel angiogenic therapeutic opportunities, since revascularization of ischaemic tissues with local delivery of VEGF has been successfully achieved in animal models, but several issues (insufficient efficiency of delivery, risk of adverse effects, and prolonged invasive procedures feasible in animals but not acceptable in patients) have limited its benefits in clinical trials.[23]

Interestingly, PlGF has also been identified as a key player in tumour resistance to anti-VEGF therapies. This led to the development of a monoclonal antibody against PlGF, which has been tested in mouse models.[31]

Tumour angiogenesis is also regulated by PDGFR, another receptor tyrosine kinase (RTK).[32] As for VEGF, PDGF signalling also plays a crucial role in the heart: a very elegant and comprehensive study[12] shows how knock-out of PDGFR-β in cardiomyocytes leads to cardiac dysfunction, HF, and a defect in stress-induced cardiac angiogenesis. Indeed, sunitinib is the most potent concomitant inhibitor of the PDGF pathway, and it has the highest incidence of LV dysfunction and HF. Such a high incidence may also be explained by inhibition of off-target kinases. One of these kinases is the ribosomal S6 kinase (RSK) family: its inhibition would suppress RSK inhibitory phosphorylation of the proapoptotic factor BAD, leading to activation of the intrinsic apoptotic pathway and possibly to ATP depletion. Another off-target kinase inhibited by sunitinib is 5' AMP-activated protein kinase (AMPK; a kinase that responds to energy stress). The myocardium is very metabolically active, and AMPK inhibition would worsen ATP depletion. These effects result in energy compromise and cardiomyocyte dysfunction.[32] In agreement with this, a very recent paper[33] shows direct contractile effects of sunitinib on different experimental myocardial preparations. Sunitinib elicited a dose-dependent negative inotropic effect in myocardium, accompanied by a decline in intracellular Ca^{2+}. Myofilament Ca^{2+} sensitivity was not altered, and there was increased reactive oxygen species (ROS) generation.

The VEGF and PDGF pathways are inhibited not only by sunitinib, but also by sorafenib. This multitargeted kinase inhibitor also blocks RAF-1 and BRAF kinase activity, disrupting ERK signalling, important for myocyte survival during stress conditions.[32] Indeed, in a mouse model, cardiac deletion of RAF-1 brought about dilation and reduced contractility, with increased myocyte apoptosis and fibrosis.[34]

Potential mechanisms for cardiovascular toxicities of the three best known antiangiogenic drugs are summarized in *Table 1*.[6,35]

Importance of cardiovascular risk factors in cancer patients requiring treatment with vascular endothelial growth factor inhibitors

Cancer patients with cardiovascular side effects due to anticancer drugs should be treated jointly by Cardiologists and Oncologists. In patients with an indication for antiangiogenic therapy, a first step would be to assess the cardiovascular risk. This should be done on the basis of the identification of concomitant cardiovascular diseases and potential cardiovascular complications before such therapies are started, considering that pre-existing hypertension and heart diseases are common in cancer patients.

Indeed, in 75 patients with imatinib-resistant metastatic stromal tumours Chu and colleagues[13] reported an 11% incidence of cardiovascular events, including two cases of MI and six of symptomatic HF, with a 28% incidence of asymptomatic LV dysfunction (absolute reduction in EF >10%). In this study, 75% of patients with a history of CAD had a sunitinib-induced cardiovascular event vs. 7% of patients without prior coronary events. Endomyocardial biopsies showed swollen mitochondria and cardiomyocyte hypertrophy, cytochrome *c* was released into the cytosol, and activation of caspase-9 led to cell death. Troponin I was moderately increased in 18% of patients.

Interestingly, the only significant univariate associations for the composite cardiovascular endpoint of cardiovascular death, MI, and HF were history of hypertension and history of CAD. Multivariable logistic regression analysis suggested that history of CAD was the only significant independent predictor of a cardiovascular event. The only significant univariate association for predictors of HF was history of CAD. In the same paper, cardiomyocyte apoptosis was increased only in mice treated with sunitinib and phenylephrine (to induce hypertension), and not in animals treated with sunitinib alone.

These data confirm that pre-existing cardiovascular conditions are risk factors for sunitinib-induced LV dysfunction. In particular, angiogenetic effects of anticancer drugs would appear extremely relevant in the setting of pre-existing LV dysfunction/HF, given the fact that (subendocardial) ischaemia and microvascular dysfunction are often present and play a big role in this setting even in the absence of coronary disease.[36,37] In conclusion, effective co-treatment for cardiovascular diseases is warranted in cancer patients with cardiovascular risk factors requiring antiangiogenic drugs.

In recent years, the connection between renal disease and HF has been brought more and more into focus. VEGF is expressed in the kidney by glomerular podocytes, and glomerular endothelial cells express VEGFRs. Podocyte-specific heterozygosity for VEGF-A causes proteinuria and capillary endotheliosis in rodents,[38] and disrupted glomerular VEGF signalling is strongly implicated in the pathogenesis of human pre-eclampsia.[39]

Table 1 Summary of the characteristics and cardiovascular side effects of the main antiangiogenic drugs

Drug	Area of application	Targets	Adverse effects	Frequency	Mechanism	Reversibility
Bevacizumab	Advanced lung, breast, colon–rectum carcinoma	Circulating VEGF	Contractile dysfunction/HF	Low	Hypertension	Reported
			Hypertension	Moderate, dose dependent	Endothelial dysfunction	Unknown
			Thrombo-embolism	Moderate	Endothelial dysfunction	Variable
Sunitinib	Renal cell cancer, GIST	VEGFR, PDGFR, c-Kit, CSF-1R, FLT3, RET, and >50 others	Contractile dysfunction/HF	Low	Mitochondrial dysfunction	Partial
			Hypertension	Moderate, dose dependent	Endothelial dysfunction	Unknown
			Thrombo-embolism	Moderate	Endothelial dysfunction	Variable
			Arrhythmia/QT prolongation	Rare	HERG K+ blockade	Unknown
Sorafenib	Renal cell cancer, hepatocarcinoma	VEGFR, PDGFR, c-Kit, FLT3, Raf-1/B-Raf and >15 others	Contractile dysfunction/HF	Rare	Cell signalling, survival block	Unknown
			Hypertension	Moderate, dose dependent	Endothelial dysfunction	Unknown
			Thrombo-embolism	Moderate	Endothelial dysfunction	Variable

Modified from Cheng and Force[6] and Suter and Ewer.[35]

PDGF-β may also play a role in restructuring the foetoplacental vasculature.[40] Also, it has to be considered that in late gestation the placenta itself secretes VEGF inhibitors such as soluble FLT1 (sFLT1). Thus, multiple gestations and pre-eclampsia may potentiate this phenomenon. Patten and colleagues[41] recently showed that in women with pre-eclampsia, subclinical cardiac dysfunction correlates with circulating levels of sFLT1. Interestingly, sFLT1 administered to wild-type mice produced diastolic dysfunction, while it caused a more profound systolic dysfunction in mice lacking cardiac PGC-1α (a regulator of VEGF expression in skeletal muscle[42,43]). These data further support the hypothesis that interplay between pre-eclampsia pathogenic factors and loss of compensatory factors in a stressed ventricle, through PDGFR and VEGFR inhibition with sunitinib, might induce cardiac dysfunction.

All in all, clinicians need to recognize and treat cardiovascular risk factors (hypertension, diabetes, current and previous cardiovascular disease, subclinical organ damage previously documented by ECG, echocardiography, or carotid ultrasound study, established or subclinical renal disease, age, smoking, dyslipidaemia, family history of premature cardiovascular disease, and abdominal obesity) in order to allow long-term continuous therapy with antiangiogenic drugs.[5] In these patients, a thorough history and examination, with ECG and blood pressure measurement, are absolutely indicated. The Cardiovascular Toxicities Panel of the National Cancer Institute (NCI) recommends avoiding administration of antiangiogenic drugs in patients with unstable myocardial ischaemia or recent infarction or thrombotic event, uncontrolled HF, arrhythmias or hypertension, or significant QT prolongation.[5]

Assessment and diagnosis of cardiovascular side effects induced by cardiotoxic antiangiogenic drugs

Sunitinib, pazopanib, and especially vandetanib may increase the risk of QT prolongation and Torsades de pointes.[5] Sunitinib and pazopanib should be used with caution in the presence of a history of QT prolongation or concomitant antiarrhythmic treatments, bradycardia, or electrolyte unbalances, while in such conditions vandetanib should be completely avoided. When vandetanib is used, an ECG should be performed at baseline, at 2–4 weeks, and at 8–12 weeks after the beginning of treatment, and every 3 months thereafter.[5]

In the presence of asymptomatic ECG ischaemic ST- and T-wave changes, the Cardiovascular Toxicities Panel of the NCI recommends suspension of antiangiogenic treatment. After advanced cardiac testing, the decision to resume oncological therapies with aggressive supporting care is subordinated to the fact that benefits should outweigh risks: this decision should be taken after a consultation between Cardiologists and Oncologists. The presence of angina or MI is *per se* a strong indication for discontinuation of antiangiogenic therapies.[5]

Hypertension is the most common side effect observed in patients on VEGF inhibitors. This is a class effect of such drugs, reported in every trial involving these inhibitors.[44] The incidence of hypertension varies according to the use of different inhibitors

(Supplementary material, *Table S1*). The Cardiovascular Toxicities Panel of the NCI recommends weekly blood pressure monitoring during the first cycle of anti-VEGF drugs (indeed, drug-related increases in blood pressure are more common early in treatment), and then at least every 2–3 weeks for the duration of the entire treatment.[44] Interestingly, the occurrence of hypertension can be considered a sort of pharmacodynamic marker of antitumour response during anti-VEGF therapy. In the work of Scartozzi and colleagues[45] on metastatic colorectal cancer patients, 20% of patients developed grade 2–3 hypertension. A partial remission was observed in 75% of patients with bevacizumab-related hypertension and in only 32% of those without hypertension. Furthermore, patients who developed grade 2–3 hypertension had a significantly longer progression-free survival than non-hypertensive patients.[45]

An interesting study[46] evaluated the association of VEGF genotype with efficacy and toxicity in the E2100 phase III study (paclitaxel vs. paclitaxel plus bevacizumab in metastatic breast cancer). An association between specific VEGF genotypes and median overall survival as well as grade 3–4 hypertension was observed with bevacizumab. Patients with such VEGF genotypes were expected to have a better antitumour response, but also an increase in blood pressure and possibly a decrease in EF.[46]

The rate and reversibility of cardiotoxicity induced by sunitinib and sorafenib were not specifically pursued in phase III trials. Most of the data concerning identification of cardiac side effects derive from retrospective analyses.[35] Only in the study of Schmidinger and co-workers[20] was cardiotoxicity assessed prospectively, after elevated cardiac enzymes and ECG abnormalities were observed in the first 10 patients. Other studies are needed to investigate cardiotoxicity in detail. In contrast to the many studies published on trastuzumab,[47] no specific publication on the potential adverse effects of antiangiogenic drugs on LV function has been published to date. On these grounds, we believe that serial EF monitoring should be performed at least in patients at risk of developing cardiotoxic effects. Echocardiography should be the strategy of choice, for its easy and relative inexpensive feasibility. Nevertheless, traditional echocardiographic indexes of cardiac function, namely fractional shortening and EF, may underestimate subtle alterations in heart function. Indeed, the heart has a tremendous recruitable contractile capacity; therefore, in order for depressed EF to be manifested, the loss of large portions of viable myocardium is needed.[48] As with investigations involving trastuzumab,[4,49,50] more clinical and experimental studies are also necessary in the case of antiangiogenic drugs, in order to compare traditional echocardiography with tissue velocity indexes and speckle tracking, real-time 3D echocardiography and multiple gated acquisition (MUGA) scanning, and magnetic resonance. The use of biomarkers (troponins and natriuretic peptides)[51,52] should be further investigated in this setting, too.

Management

The Cardiovascular Toxicities panel of the NCI recommends that patients who develop stage I hypertension ($\geq$140/90 mmHg or increases in diastolic blood pressure of $\geq$20 mmHg from baseline) should start antihypertensive treatment, or have their current therapy titrated to better control, or have another agent added.[44] ACE inhibitors can lower blood pressure relatively rapidly, while some dihydropiridine Ca^{2+} channel blockers can take 3–5 days to achieve their effect. Therefore, ACE inhibitors and ARBs are to be preferred, especially in view of the fact that they are effective in preventing HF. For this same reason, the use of beta-blockers is encouraged. In particular, carvedilol also shows antioxidant properties, with a positive impact on cardiac mitochondria, protecting myocytes against mitochondrial cardiomyopathy.[53] Indeed, carvedilol was the beta-blocker of choice in the Cochrane database[54] with anthracyclines, and was also used with trastuzumab.[51] However, other beta-blockers need to be tested, and might be found to be more effective.

According to the 2009 Focused Update of the American Heart Association (AHA) HF guidelines, in order to prevent the onset of HF, patients on antiangiogenic drugs should be considered as stage A HF patients.[55] This stage identifies patients at high risk of developing HF, but without structural heart disease or symptoms of HF as yet. On such a basis, patients on cardiotoxic agents (i.e. antiangiogenic drugs) should undergo non-invasive evaluation of LV function with imaging tests and biomarkers. HF symptoms and signs should be monitored and cardiovascular risk factors should be addressed. In a recent study, the authors tried to develop a common algorithm for management of all biological anticancer drugs.[56] The group of Professor van Veldhuisen showed reduced myocardial blood flow in patients with asymptomatic LV dysfunction;[57] hence such patients have to be considered with particular attention. In the case of asymptomatic LV dysfunction, a very recent paper by Suter and Ewer[35] suggests continuing angiogenesis inhibitors with mild (EF decrease >15%, with EF >50%) or moderate (EF 50–40%) dysfunction, checking always for hypertension. Only in severe (EF <40%) LV dysfunction is it recommended to stop cancer therapy, discuss alternative drugs, and treat LV dysfunction (*Figure 2*).

Symptomatic patients should be treated with ACE inhibitors; diuretics and nitrates should be used with fluid retention. Beta-blockers should be started 3–4 weeks after symptoms, once the patient is stable, with titration of ACE inhibitors and beta-blockers to the highest tolerated dose. After the EMPHASIS-HF trial,[58] the recent 2012 Heart Failure Association (HFA) of the European Society of Cardiology (ESC) guidelines[59] have extended the indication for aldosterone receptor antagonists also to NYHA II patients with EF <35%. Also, CRT can be beneficial already in NYHA II patients with a life expectancy >1 year in good functional status and sinus rhythm, and with EF $\leq$ 30%.

Antiangiogenic drugs should then be resumed upon EF improvement and normalization, but the issue of reversibility of LV dysfunction, and the opportunity for re-administration of VEGF inhibitors after improvement from NYHA III–IV is still unclear. In the work of Schmidinger and colleagues,[20] all symptomatic patients discontinued the inhibitors, and started medical cardiac treatment. They all recovered, but three patients showed abnormal cardiac enzymes throughout the whole TKI treatment. All 11 patients on sunitinib, and 11 out of 14 patients on sorafenib could resume therapy. Patients who resumed TKIs in combination with cardiovascular drugs did not show more relevant cardiac events. However, it remained unclear whether recovery had been obtained because of interruption of anticancer treatment or

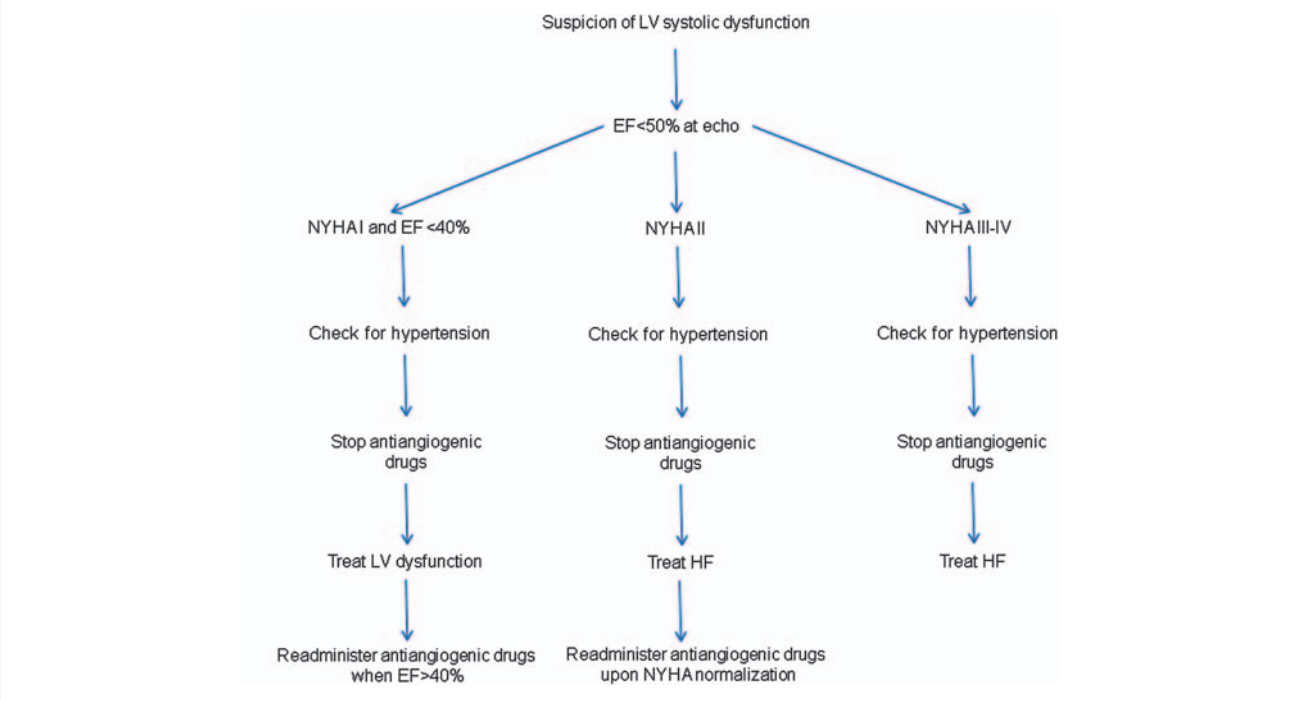

Figure 2 Considerations for management of LV dysfunction and heart failure induced by antiangiogenic therapies. Modified from Suter and Ewer[35] and Ederhy *et al.*[56]

thanks to cardiovascular therapies. In contrast to the very high rate of recovery observed in this study, in another work[16] seven patients (15%) experienced symptomatic grade 3/4 LV dysfunction with sunitinib; in spite of discontinuation of sunitinib and initiation of HF therapy, three patients had persistent cardiac dysfunction.

Concluding remarks

Patients with cardiotoxicity from oncological treatments should be monitored closely by both Cardiologists and Oncologists.[4,35,56] The 2012 HFA ESC guidelines do not specifically mention antiangiogenic drugs. However, they recommend pre- and post-evaluation of EF in patients on anticancer cardiotoxic drugs, and discontinuation of such treatments upon development of LV dysfunction, with initiation of HF therapies.[59] Therefore, cancer patients should be treated according to the standard guidelines. As we previously discussed for trastuzumab, new strategies for early detection[4] and for prevention of cardiotoxicity from antineoplastic drugs are needed. This is an area of active research.[60] Correction of cardiovascular risks factors is mandatory, and as trials on antiangiogenic drugs with cardiotoxic effects are being performed (NCT01370109, NCT00532064, and NCT01246778, clinicaltrials.gov), we agree with Schmidinger and colleagues[20] that an '*a priori*' cardiac protection with ACE inhibitors could be started together with angiogenesis inhibitors. Protecting the heart from cardiotoxic effects of antiangiogenic drugs will favour the administration of these highly beneficial therapeutics.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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