ORIGINAL ARTICLE

Effects of antiangiogenic chemotherapy on cardiac function - the added value of myocardial deformation imaging

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Abstract: The use of antiangiogenic therapy has become an important therapeutic tool in oncology, leading to significantly improved outcomes. But, as its use expanded, it has become increasingly recognized that it also induces a wide spectrum of toxicities, including cardiovascular, at higher than anticipated rates. We conducted a prospective study including 45 consecutive oncologic patients (31 men, (68.8%), with a mean age of 60.7±9.7 years (men 61.2±7.9, women 59.5±13.1)), with digestive and renal malignant tumors, receiving antiangiogenic therapies (bevacizumab, sunitinib, sorafenib), aiming to characterize the complex cardiovascular response to antiangiogenic agents, focusing mainly on cardiac dysfunction and arterial hypertension (HTN) and on the possible link between them. Patients were evaluated before the start of the antiangiogenic therapy, at one month after they started the treatment, and then at 3-month intervals. The main findings of the present study were that antiangiogenic therapy induces worsening of pre-existing HTN or *de novo* HTN and also a reduction in all systolic function parameters of both ventricles, in almost half of the studied patients, stressing that it is important to assess both ventricles during cancer therapy. Although antiangiogenic therapy induced HTN may seem an obvious mechanism leading to myocardial dysfunction, it is probably not the primary one, as we did find neither causality nor association between de novo HTN and left ventricular dysfunction. We did find, however, that pre-existing HTN represents a major risk factor for patients receiving antiangiogenic treatment, as it usually gets worse and difficult to control, and correlates statistically with reductions in left ventricular ejection fraction meeting the cardiotoxicity criteria. It also tends to induce more frequent reductions of the global longitudinal strain of both left and right ventricles, but above the statistically significant level. Left ventricular systolic dysfunction induced by antiangiogenic agents should not be regarded as a consequence of HTN, but as rather related to the intrinsic myocardial toxicity of these agents, pre-existing HTN being probably a major permissive/precipitating factor.

Keywords: antiangiogenic therapy, anti-VEGF agents, bevacizumab, sunitinib, sorafenib, cardiovascular toxicities, arterial hypertension, global longitudinal strain, ejection fraction, myocardial function, speckle tracking echocardiography

Rezumat: Având în vedere utilizarea din ce în ce mai frecventă a terapiei antiangiogenice în oncologie și toxicitatea sa cardiovasculară mai puțin studiată, ne-am propus evaluarea țintită a efectelor cardiovasculare toxice ale tratamentului antiangiogenic, axându-ne în principal pe disfuncția cardiacă și hipertensiunea arterială și pe posibila legătură dintre acestea. Am derulat un studiu prospectiv în care am înrolat 45 de pacienți oncologici (31 bărbați, (68.8%), cu vârsta medie de 60.7±9.7 ani (bărbați 61.2±7.9 ani, femei 59.5±13.1 ani)) cu neoplazii în sfera digestivă și renală, tratați cu agenți antiangiogenici (bevacizumab, sunitib și sorafenib). Pacienții au fost evaluați cardiologic înainte de începerea tratamentului, la o lună de la începerea tratamentului și apoi la intervale de 3 luni. Principalele rezultate ale studiului efectuat indică faptul că, la aproape jumătate din pacienții studiați, tratamentul antiangiogenic induce hipertensiune arterială de novo sau agravarea hipertensiunii arteriale preexistente, precum și alterarea parametrilor de funcție sistolică ai ambilor ventriculi. Aceste rezultate subliniază importanța monitorizării funcției biventriculare la pacienții oncologici în cursul chimioterapiei. Cu toate că hipertensiunea arterială indusă de tratamentul antiangiogenic poate părea mecanismul evident al disfuncției miocardice, probabil că nu este singurul mecanism, datele din literatură precum și rezultatele studiului prezentat neobservând o asociere sau cauzalitate între hipertensiunea arterială *de novo* și disfuncția cardiacă. Am observat însă că hipertensiunea arterială preexistentă reprezintă un factor de risc major pentru pacienții care primesc tratament antiangiogenic. Aceasta este de obicei agravată de

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tratamentul antiangiogenic, devine dificil de controlat cu tratament antihipertensiv şi s-a corelat semnificativ cu reducerile fracţiei de ejecţie a ventriculului stâng sugestive pentru cardiotoxicitate. În plus, hipertensiunea arterială preexistentă agravată de tratamentul antiangiogenic favorizează reducerea semnificativă a strainului global longitudinal pentru ambii ventriculi, corelaţia fiind însă peste pragul de semnificaţie statistică. Disfuncţia miocardică indusă de agenţii antiangiogenici nu ar trebui privită ca o simplă consecinţă a hipertensiunii arteriale, ci ca fiind fiind probabil factorul precipitant/ permisiv major al toxicităţii miocardice intrinseci a acestei terapii.
Cuvinte cheie: tratament antiangiogenic, bevacizumab, sunitinib, sorafenib, toxicitate cardiovasculară, hipertensiune arterială, strain global longitudinal, fracţie de ejecţie, difuncţie miocardică biventriculară.

INTRODUCTION

As survival of oncologic patients has significantly improved, the cardiac toxicity of oncologic treatments has become an increasingly challenging issue, both for oncologists and cardiologists. According to the concept of an "angiogenic switch", the induction of angiogenesis is a key step in tumor growth and metastasis and it is mainly controlled by the vascular endothelial growth factor (VEGF)[1,2]. The VEGF signaling pathway has thus become an important therapeutic target in oncology, and the use of anti-VEGF agents has led to significantly improved outcomes in a variety of advanced solid tumors[3]. But, as the use of antiangiogenic therapy expanded, it has become recognized that it also induces a wide spectrum of toxicities, including cardiovascular complications (arterial hypertension (HTN), arterial and venous thromboembolic events, QTc interval prolongation, left ventricular dysfunction, and myocardial ischemia), at higher than anticipated rates[4,5]. Moreover, as these agents mainly target the endothelial cells rather than the tumor cells themselves, many of their toxicities are unique from the ones reported with conventional chemotherapy agents.

In this context, knowing the possible cardiac toxicities of these agents and understanding their underlining mechanisms becomes highly important. As almost all of the existing studies on anti-VEGF therapy were not designed with standardized cardiac endpoints, and only clinically significant cardiovascular events were recorded, the actual incidence of the cardiotoxicity of these agents in unselected cancer patient populations remains yet unknown and highlights the importance of further prospective studies with appropriate cardiovascular surveillance.

The aim of our study was to characterize the complex cardiovascular response to anti-VEGF agents, focusing mainly on cardiac dysfunction and its determinants.

METHODS

Study population

During January 2015 and January 2016, we conducted a prospective study including consecutive oncologic patients, with digestive and renal malignant tumors, receiving anti-VEGF therapies (bevacizumab, sunitinib, sorafenib), referred from the Oncology Department of the "Fundeni Clinical Institute" to the Cardiology Department and EuroEchoLab of the " Prof. Dr. C.C. Iliescu" Institute for Cardiovascular Diseases.

Exclusion criteria for our study were: non-sinus rhythm, more than moderate valvular heart disease, known coronary artery disease, low echogenicity for optimal echo data acquisition. The study protocol was approved by the institutional Research Ethics Board.

Clinical Data

Patients were evaluated before the start of the anti-VEGF therapy (Visit 1), at one month after they started the treatment (Visit 2), and then at 3-month intervals (Visits 3 and 4). The following clinical data were collected: age, gender, history of smoking, HTN (defined as a history of HTN requiring medical therapy), diabetes mellitus, and hypercholesterolemia. Functional status was defined according to the *New York Heart Association* (NYHA) classification.

Echocardiography

The transthoracic echocardiography examination was performed by the same operator, using a GE Vivid E9 Ultrasound Machine (GE Vingmed Ultrasound AS, Horten, Norway). All 2D and Doppler images were digitally stored as three consecutive cycles, while one cycle was stored for 3D images. All echocardiographic data were analyzed offline using a commercially available software package (EchoPAC PC version BT12; GE Medical Systems, Milwaukee, WI) by a single observer (AMPV). Transmitral flow velocities were measured from the apical four chamber view using conventional pulsed-wave Doppler imaging. Left ventricular ejection fraction (LVEF) was calculated using the modified

biplane Simpson's method by 2D echocardiography. Tricuspid annular plane systolic excursion (TAPSE) was obtained using an M-mode cursor passed through the tricuspid lateral annulus in a four-chamber view and measuring the amount of longitudinal displacement of the annulus at peak-systole. Peak systolic (S') and peak early diastolic (E') mitral annular velocities were obtained by pulsed-wave tissue Doppler imaging (TDI) from the apical four-chamber view, using the septal and the lateral sites. Peak systolic velocity of the tricuspid annulus (RV free wall S') was obtained by pulsed-wave TDI, in the view that achieved parallel alignment of the Doppler beam with the RV free wall. Analysis of myocardial global longitudinal strain (GLS) was performed offline for both the left ventricle (LV) and right ventricle (RV), by the speckle tracking technique using commercially available software (automated function imaging (AFI)). The apical 4-, 3-, and 2-chamber images of the LV were used for the calculation of the LV GLS (16-segment model) and an apical 4-chamber view of the RV was used for the calculation of RV GLS (6-segment model).

We defined cardiotoxicity as a decrease in the 2D LVEF of >10 percentage points from baseline or to a value <53%[6,7]. For the LV GLS, we interpreted that a >15 relative percentage reduction from baseline may suggest the risk of cardiotoxicity[7]. For the RV GLS, we tested the significance of arbitrary cutoffs of >15 and 20 relative percentage reductions from baseline.

Ambulatory blood pressure monitoring

All patients had a 24 hours ambulatory blood pressure (BP) monitoring (ABPM) at Visits 1, 2, 3 and 4. Average 24-hours, average daytime, and nighttime, as well as maximal BP values, were noted at each visit. We used a value above 130/80 mmHg of the average 24-hours blood pressure, on the 24 hours ABPM, to identify patients having arterial hypertension (HTN). All patients identified as having HTN at any time during the study received antihypertensive treatment with beta-blockers, angiotensin-converting enzyme inhibitors, and/or calcium channel blockers, based on the treating physician options.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for processing the data. We used the Chi-square test (χ_2) to assess the influence of the factors considered to measure cardiotoxicity over the other factors. It is a statistical test that shows if two factors are independent or not, and was used to interpret incidence tables generated by cross tabulation of the categorical coding of the recorded variables. Because the study involved comparisons between numerical data, we used either Student's *t* test (for 2 groups) or ANOVA (for 3 or more groups) to compare the mean values of the analyzed parameters. If the ANOVA test result was statistically significant, we continued the analysis with "*post hoc*" tests, such as Fisher's LSD tests, to identify pairs of categories which had significant differences. A p value <0.05 was considered significant.

RESULTS

Study population characteristics

We included in the study 45 patients (31 men, 68.8%), with a mean age of 60.7±9.7 years (men 61.2±7.9, women 59.5±13.1, p=0.58). The baseline characteristics of the patients are presented in Table 1. During the study, 18 patients died due to oncologic causes and 9 patients were lost to follow-up. Overall, 45 patients completed Visits 1 and 2, only 34 patients completed Visit 3 and only 18 patients completed Visit 4.

Left ventricular function parameters

All patients had preserved 2D derived LVEF (≥53%) at the beginning of the anti-VEGF therapy. During the course of antiangiogenic therapy, there was a statistically significant reduction in the parameters that are used to identify left ventricular systolic dysfunction: 2D LVEF, mean LV S' value and LV GLS (Table 2). We found no statistically significant variations in the parameters that are used to characterize left ventricular diastolic function: E/A and E/E' values (Table 2).

Seven patients (15.5%) presented with cardiotoxicity criteria during follow-up at Visit 2 (2D LVEF dropping from 63.8% ± 8.6% to 54.0% ± 7.2%, p=0.039), but were clinically asymptomatic. A reduction in the LV

Table 1. Baseline characteristics of study population

Parameter	Value
Number of patients	45
Male sex (n, %)	31 (68.9%)
Mean age of patients (years)	60.8 ± 9.7
Type 2 diabetes mellitus	5 (11.1%)
Smoking (n, %)	19 (42.2%)
Preexisting HTN (n, %)	20 (44.4%)
Prior chemotherapy (n, %)	13 (28.9%)
Digestive malignancy (n, %)	37 (82.2%)
Renal malignancy (n, %)	8 (17.8%)
Malignancy with metastasis	45

Table 2. Left ventricular function parameters evolution during follow-up

Parameters of LV function	Visit 1	Visit 2	Visit 3	Visit 4	p ANOVA
No. of patients	45	45	34	18	
2D LVEF	63.4%±5.1%	60.4%±5.3%*	60.7%±5.2%*	61.8%±5.4%	p=0.03
Mean S' value	7.88 ± 1.32	7.0 ± 1.5*	7.1 ± 1.0*	7.1 ± 1.2*	p=0.01
LV GLS	-18.97%±2.02%	-17.3%±2.3%*	-16.5%±2.1%*	-17.3%±1.6%*	p<0.001
E/A	0.96±0.31	0.93±0.30	0.90±0.34	0.90±0.25	p=0.77
E/E'	9.83±4.23	9.78±2.97	9.01±2.36	8.71±3.14	p=0.48

* p (*post hoc* Fisher LSD) <0.05 versus baseline.

Table 3. Comparison between the presence of cardiotoxicity and the reductions in other LV systolic function parameters

	Reductions in 2D LVEF that met the cardiotoxicity criteria	Reductions in the LV GLS of more than 15% from baseline, anytime	Mean S' value <8, anytime
Yes	7	7 (100%)	7 (100%)
No	38	15 (39.5%)	31 (81.6%)
Total	45	22 (48.9%)	38 (84.4%)
p Fisher	-	0.004	0.278
p Chi2	-	0.032	0.216

GLS of more than 15% from baseline was present in 22 patients (48.8%) at different time-points: 10 patients at Visit2; 20 patients at Visit 3 (12 new patients and 8 patients that had a reduction also at Visit 2) and 2 patients at Visit 4 (who had also presented a reduction at Visit 3).

When comparing the reductions in the LV GLS (of more than 15% from baseline) or in the mean S' value (below 8 cm/s) with the reductions in 2D LVEF (that met the criteria for cardiotoxicity), we found that the reductions in 2D LVEF correlate with the reductions in the LVGLS, but not with the reductions in the mean S' value (Table 3).

Right ventricular function parameters

Regarding the RV, we noted a statistically significant reduction, mainly until Visit 3, in the parameters of RV systolic function: TAPSE, RV free wall S', and RV GLS (Table 4).

By comparing the percentage reduction (vs baseline) of the LV GLS and RV GLS, we noticed that the reduction of the RV GLS was significantly higher than that for the LV GLS (-13.5±13.6% vs -8.2±9.4%, p=0.03). As this reduction was observed very early (from Visit 2) after the start of the antiangiogenic treatment, we could not analyze if the RV GLS is affected earlier than the LV GLS (Figure 1).

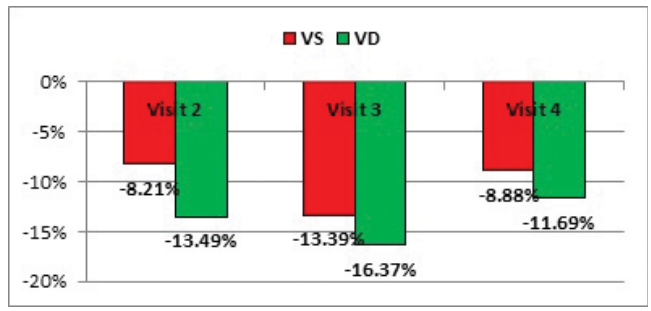

Figure 1. Comparison between the reductions from baseline of RV GLS and LV GL, during the antiangiogenic treatment (p value for Visit 2 =0.036; p value for Visit 3= 0.387; p value for Visit 4 = 0.644).

Arterial hypertension

Using ABPM, 14 patients (31.11%) had pre-existent HTN at baseline (Visit1), and they received antihypertensive treatment. After the start of the antiangiogenic treatment, only 2 of these patients presented optimally controlled BP values with medical treatment, while the rest of 12 patients (26.67%) presented worsening BP levels and needed further titration of the medication. During the antiangiogenic treatment, 13

Table 4. Right ventricular systolic function parameters

Parameters of RV systolic function	Visit 1	Visit 2	Visit 3	Visit 4	p ANOVA
No. of patients	45	45	34	18	
TAPSE	23.18 ± 3.81	21.09 ± 3.19*	21.06 ± 3.59	22.56 ± 2.99	p=0.0129
RV free wall S'	15.00 ± 3.43	13.47 ± 2.69*	13.14 ± 2.99*	13.31 ± 2.93	p=0.0259
RV GLS	-23.08%±2.78%	-20% ± 4.19%*	-19.54%±3.99%*	-20.34% ±4.56%	p=0.0001

* p (*post hoc* Fisher LSD) <0.05 versus baseline

Table 5. HTN in the studied patients		
HTN	**No. of patients**	**%**
Patients with HTN at baseline (Visit 1)	14	31.11
Patients with HTN at baseline (Visit 1), and who presented worsening or suboptimal control of BP values during the anti-VEGF therapy	12	26.67
Patients with de novo HTN during the anti-VEGF therapy (who did not present HTN at baseline)	13	28.89

patients (28.89%), who did not present HTN at baseline, developed *de novo* HTN and were also started on antihypertensive medication (Table 5).

Arterial hypertension and ventricular function parameters

When comparing the influence of HTN on the reduction in ventricular function parameters, we noticed that a reduction of LV GLS (of more than 15% from baseline) was more frequently encountered in patients with HTN at baseline, compared with patients who developed de novo HTN or patients with normal BP values. But, when testing the statistical significance of this observation, the result of the *p* Chiχ_2 test was 0.096 (above the maximum admitted cutoff of 0.05) (Figure 2). The same observation is true for a reduction of RV GLS (of more than 20% from baseline), but the differences are even more subtle (*p* Chiχ_2 test= 0.332 >0.05) (Figure 3). However, for the reductions in the 2D LVEF (decrease of >10 percentage points from baseline, or to a value <53%), the observed differences are statistically significant, patients with HTN at baseline being more prone to develop cardiotoxicity (*p* Chiχ_2 test=0.030 < 0.05) (Figure 4).

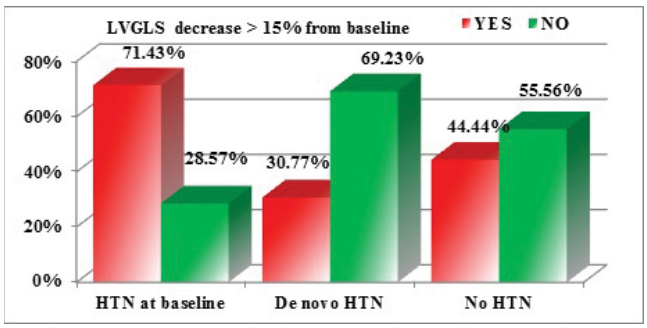

Figure 2. Correlations between the reduction of the LV GLS and the presence/development of HTN (p Chi χ_2=0.096 >0.05).

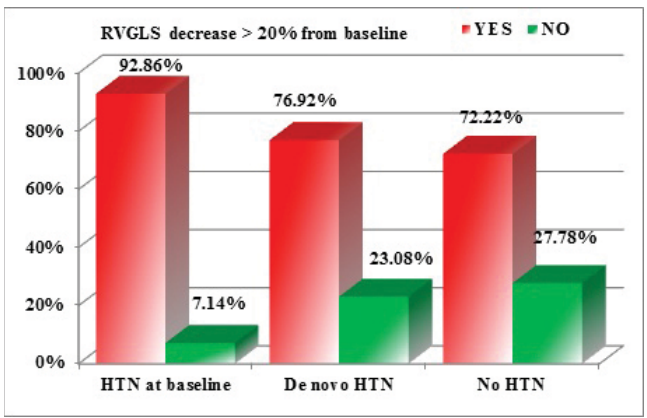

Figure 3. Correlations between the reduction of the RV GLS and the presence/development of HTN (p Chi χ_2=0.332 >0.05).

Influence of treatment doses, diabetes mellitus and age on the incidence of HTN and LV/RV systolic dysfunction

We also considered the doses of the anti-VEGF agents and tried to see if there is any correlation with the incidence of toxicities. We divided our patients into two groups:

- group A: patients who received smaller doses of anti-VEGF agents (bevacizumab 5 mg/kg or sorafenib 400 mg or sunitinib 37.5 mg)
- group B: patients who received higher doses of anti-VEGF agents (bevacizumab 7.5 mg/kg or sorafenib 800 mg or sunitinib 50 mg).

We found a significant statistical difference among the two groups, patients in group B presented a higher incidence of worsening HTN or *de novo* HTN and a higher incidence of significant reductions in LV GLS (with more than 15% from baseline) and in RVGLS (with more than 20% from baseline). We found no significant statistical difference regarding the reductions in 2D LVEF that met the cardiotoxicity criteria (Table 6).

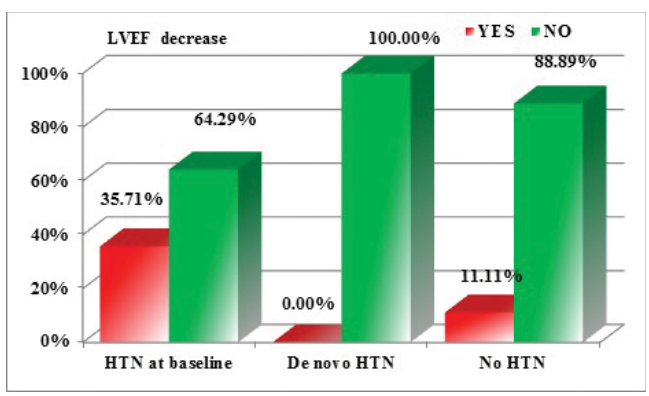

Figure 4. Correlations between the reduction of the 2D LVEF and the presence/development of HTN (p Chi χ_2=0.030 <0.05).

Table 6. Correlations between antiangiogenic treatment doses and the incidence of cardiovascular toxicities

	Group A: (n=26 pts) Low anti-VEGF doses	Group B: (n=19 pts) High anti-VEGF doses	p
Worsening HTN or de novo HTN	11 (42.31%)	14 (73.68%)	0.036
Reduction in 2D LFEV - cardiotoxicity	5 (19.23%)	2 (10.53%)	0.359
Reduction in LV GLS >15% from baseline	9 (34.62%)	13 (68.42%)	0.026
Reduction in RV GLS >20% from baseline	11 (42.31%)	14 (73.68%)	0.036

We also found that patients with prior chemotherapy presented a higher incidence of significant reductions in LV GLS (with more than 15% from baseline) but not a higher incidence of worsening HTN, *de novo* HTN, reductions in 2D LVEF (that met the cardiotoxicity criteria) or reductions in RV GLS (with more than 20% from baseline) (Table 7).

There were no statistically significant correlations between the reductions in LV GLS, RV GLS, 2D LVEF or worsening/*de novo* HTN and the presence of diabetes mellitus or with age above 60 years old (Table 8).

Also, there were no differences between the three types of antiangiogenic agents used and the reductions in LV GLS, RV GLS, 2D LVEF, TAPSE or worsening/de novo HTN (Table 9 and Table 10).

DISCUSSIONS

The main findings of the present study were that antiangiogenic therapy induces *de novo* HTN or worsening of pre-existing HTN and, also, a reduction in the systolic function parameters of both ventricles in almost half of the studied patients, stressing that

Table 7. Correlations between prior chemotherapy and the incidence of cardiovascular toxicities

	Prior chemotherapy (n=13 pts)	No prior chemotherapy (n=32 pts)	p
Worsening HTN or de novo HTN	7 (53.85%)	18 (56.25%)	0.68
Reduction in 2D LFEV - cardiotoxicity	4 (30.77%)	3 (9.38%)	0.09
Reduction in LV GLS >15% from baseline	10 (76.92%)	12 (37.50%)	0.018
Reduction in RV GLS >20% from baseline	9 (69.23%)	17 (53.12%)	0.257

Table 8. Correlations between the presence of diabetes mellitus or age above 60 years old and the incidence of cardiovascular toxicities

	Cases	Reduction in LV GLS >15% from baseline	Reduction in 2D LVEF - cardiotoxicity	Worsening HTN or de novo HTN	Reduction in RV GLS >20% from baseline
Diabetes mellitus					
yes	5	3 (60.00%)	0 (0.00%)	4 (80.00%)	3 (60.00%)
no	40	19 (47.50%)	7 (17.50%)	21 (52.50%)	23 (57.50%)
Total	45	22 (48.89%)	7 (15.56%)	25 (55.56%)	26 (57.78%)
p Fisher	-	0.478	0.411	0.251	0.650
Age >60 years					
yes	20	12 (60.00%)	2 (10.00%)	14 (70.00%)	13 (65.00%)
no	25	10 (40.00%)	5 (20.00%)	11 (44.00%)	13 (52.00%)
Total	45	22 (48.89%)	7 (15.56%)	25 (55.56%)	26 (57.78%)
p Fisher	-	0.151	0.311	0.074	0.284

Table 9. Correlations between the type of antiangiogenic treatment and the reductions in LV GLS, 2D LVEF or worsening/*de novo* HTN

Anti-VEGF agent	Cases	LV GLS <15% baseline	Reduction in 2D LFEV - cardiotoxicity	Worsening HTN or *de novo* HTN
Bevacizumab	21	13 (61.90%)	3 (14.29%)	9 (42.86%)
Sorafenib	16	5 (31.25%)	2 (12.50%)	12 (75.00%)
Sunitinib	8	4 (50.00%)	2 (25.00%)	4 (50.00%)
Total	45	22 (48.89%)	7 (15.56%)	25 (55.56%)
p Chi2	-	0.181	0.711	0.141

Table 10. Correlations between the type of antiangiogenic treatment and the reductions in RV GLS or in TAPSE value

Anti-VEGF agent	Cases	RV GLS <15% baseline	RV GLS <20% baseline	TAPSE <17 anytime
Bevacizumab	21	18 (85.71%)	15 (71.43%)	2 (9.52%)
Sorafenib	16	10 (62.50%)	9 (56.25%)	1 (6.25%)
Sunitinib	8	4 (50.00%)	2 (25.00%)	0 (0.00%)
Total	45	32 (71.11%)	26 (57.78%)	3 (6.67%)
p Chi2	-	0.106	0.076	0.653

it is important to assess both ventricles during cancer therapy. This is in line with the ASE/EACVI Expert Consensus Statement on the multimodality imaging of adult patients receiving cancer therapy recommendations, which highlight the importance of monitoring the left and also the right ventricular function parameters during cancer therapy[6].

Although *de novo* HTN induced by anti-VEGF agents may seem an obvious mechanism leading to myocardial dysfunction, it is probably not the primary one, as we did find neither causality nor association between de novo HTN and cardiac dysfunction and, to our knowledge, these were not reported in any trial. We did find, however, that pre-existing HTN represents a major risk factor for patients receiving anti-VEGF treatment, as it usually gets worse and difficult to control, and correlates statistically with reductions in LVEF meeting the cardiotoxicity criteria. It also tends to induce more frequent reductions of LVGLS and RVGLS, but above de statistically significant level.

Myocardial dysfunction induced by antiangiogenic agents should not be regarded only as a consequence of HTN, but also as rather related to the intrinsic myocardial toxicity of these agents, pre-existing HTN being probably a major permissive/precipitating factor.

HYPERTENSION AND ANTIANGIOGENIC DRUGS

Among the cardiovascular toxicities of anti-VEGF agents, HTN is the most frequent, with a reported incidence of 19% to 47%[8]. Several mechanisms have been linked to the occurrence of VEGF inhibitor-related HTN: microvascular rarefaction, decreased nitric oxide and prostacyclin production, reduced lymphangiogenesis, increased endothelin-1 production, increased arterial stiffness and renal dysfunction[9]. HTN has been reported to be a dose-dependent adverse cardiac effect, with the greatest magnitude occurring rapidly, within hours to days after the beginning of therapy, and with a rapid decrease in BP associated with the withdrawal of the anti-VEGF agents[9]. Risk factors for anti-VEGF-induced HTN remain largely unknown.

In our study, we used 24 hours Holter BP monitoring as an objective tool to identify patients having HTN. We found that 14 patients (31.11%) had pre-existent HTN before the start of antiangiogenic treatment, and they received treatment with beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. After the start of the antiangiogenic treatment, only 2 of these patients presented optimally controlled BP values with medical treatment, while the rest of 12 patients (26.67%) presented worsening BP levels and needed further titration of the medication. Moreover, 13 patients (28.89%) presented de novo HTN, probably induced by the antiangiogenic treatment, and were also started on beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers.

Regarding the possible risk factors for HTN induced by the antiangiogenic treatment, we found that patients who received higher doses of anti-VEGF agents (group B) presented a higher incidence of worsening HTN or de novo HTN than patients who received smaller doses of anti-VEGF agents (p Chiχ_2=0.0359<0.05). There was no correlation between prior chemotherapy, diabetes mellitus, and age above 60 years old or the type of antiangiogenic medication with the risk of worsening or de novo HTN.

We noticed that de novo HTN induced by antiangiogenic agents responded better to the antihypertensive medication, most of the patients achieving BP targets with the initial doses and needed no further titration of the antihypertensive medication, compared with pre-existing HTN which tended to worsen and to be difficult to control. Moreover, we found no statistical correlation between *de novo* HTN and reductions in the parameters of ventricular function, but pre-existing HTN correlated significantly with reductions in LVEF meeting the cardiotoxicity criteria (*p* Chi χ_2=0.030). It also presented the tendency to induce

more frequent reductions of LVGLS and RVGLS, but above the statistically significant level (*p* Chiχ_2=0.096 and 0.332 respectively).

We reckon *pre-existing HTN as a major risk factor for patients receiving anti-VEGF therapy, and these patients need special attention with aggressive antihypertensive treatment and a very close monitoring during antiangiogenic treatment.*

CARDIOTOXICITY OF ANTIANGIOGENIC DRUGS

Although there are no clear data on the actual incidence, pathophysiology, and reversibility of cardiac dysfunction, the potential of anti-VEGF inhibitors to induce cardiac dysfunction is certain[10]. The mechanism underlying this effect is not well understood. Although anti-VEGF induced *de novo* HTN may seem an obvious mechanism leading to cardiac dysfunction, it is probably not the primary one, and neither the causality nor association between HTN and HF/ LV dysfunction was reported in any trial[9].

In our study, during the antiangiogenic therapy, there was a significant reduction in all parameters of systolic function of both ventricles (LVGLS mean S' value of LV, 2D LVEF, RV free wall S' value, TAPSE, RVGLS).

We noticed a reduction in the LVGLS of more than 15% from baseline in 22 patients (48.88%). 7 patients (15.55%) presented a significant reduction in 2D LVEF that met the criteria for defining cardiotoxicity (as a decrease in the 2D LVEF of >10 percentage points from baseline or to a value <53%)[6,7], but they were clinically asymptomatic. When comparing the reductions in the LVGLS (of more than 15% from baseline) with the reductions in 2D LVEF (that met the criteria for cardiotoxicity) using the Chiχ_2 test, we found that the reductions in 2D LVEF correlate with the reductions in the LVGLS (p Chiχ_2 =0.032<0.05). It is important to notice that the sensitivity of this test is 100%, meaning that all patients with a decrease in 2DLVEF had, at some point, a decrease in LVGLS (specificity is 62.16%). Also, the negative predictive value of the Chiχ_2 test is 100%, which could be interpreted as such: patients that did not have a decrease in LVGLS will not have a decrease of 2DLVEF. But, this cannot be confirmed as, in our study, only 7 patients had a decrease in 2DLVEF, and all of them displayed it on Visit 2, when we had only the baseline value of LVGLS, and not an estimate evolution of LVGLS.

THE RELATION BETWEEN ARTERIAL HYPERTENSION AND CARDIAC DYSFUNCTION

We also tested for correlations between the reduction of the ventricular systolic function parameters and HTN. While de novo HTN induced by antiangiogenic treatment proved to be more easily controlled with antihypertensive medication and had no significant impact on cardiac function parameters, pre-existing HTN was identified as a major risk factor for cardiotoxicity. We noticed that a reduction in LVGLS of more than 15% from baseline was more frequently encountered in patients with HTN at baseline, compared with patients who developed *de novo* HTN or patients with normal BP values. But, when testing the statistical significance of this observation, the result of the Chiχ_2 test was 0.096 (above the maximum admitted cut-off of 0.05). The same observation is true for a reduction of RV GLS (of more than 20% from baseline), but the differences are even more subtle (*p* Chiχ_2 test= 0.332 >0.05). However, for the reductions in the LVEF (decrease of >10 percentage points from baseline, or to a value <53%), the observed differences are statistically significant, patients with HTN as baseline being more prone to develop cardiotoxicity (*p* Chiχ_2 test=0.030 <0.05).

Also, patients in group B, who received higher doses of anti-VEGF agents, presented a higher incidence of significant reductions in LVGLS (with more than 15% from baseline) than patients who received smaller doses of anti-VEGF agents (p Chiχ_2=0.0165<0.05).

These results may imply that *myocardial dysfunction induced by antiangiogenic agents should not be regarded only as a consequence of HTN, but also as rather related to the intrinsic myocardial toxicity of these agents, HTN being probably a major permissive/precipitating factor.*

VEGF is critical for capillary density in the myocardium and stem-cell differentiation into cardiomyocytes[9]. Also, preclinical studies have shown that the role of VEGF signaling in the heart extends beyond angiogenesis and that it also mediates important compensatory responses to stress and injury[9,11,12]. In animal models with hypertrophied pressure-loaded hearts, VEGF reduced apoptosis and preserved contractile function by the promotion of capillary growth[9,11,12]. In mice with pressure-overloaded hearts due to transverse aortic constriction (TAC), inactivation of endogenous VEGF led to decreased capillary density, impaired cardiac hypertrophy and loss of contractile function[9,11,13]. Thus, inhibiting the VEGF pathway in

the setting of HTN contributes to maladaptive hypertrophy of cardiomyocytes and possibly LV dysfunction[9,11,14].

Also, all parameters of RV systolic function (free wall S'; RVGLS and TAPSE) presented reductions during the antiangiogenic treatment, and this may be another possible argument for the intrinsic myocardial toxicity of these agents. Moreover, we found that patients who received higher doses of anti-VEGF agents (group B) presented a higher incidence of significant reductions in RVGLS (with more than 20% from baseline) (p=0.036) and that prior chemotherapy had no statistically significant impact on RVGLS reductions. A reduction of TAPSE below 17 mm was encountered in only 3 patients (6.66%). We tested for statistical correlations between the reductions in the RVGLS (using an arbitrary cutoffs of more than 20% from baseline) or in the right ventricular free wall S' value by TDI (below 10 cm/s) with the reductions in TAPSE value below 17 mm and we did not find any significant correlation. We also compared the percentage reduction of the GLS for the left and right ventricles and noticed that the reduction of the RVGLS was significantly higher than that for the LVGLS, (*t* Student test p=0.0336 <0.05). It may be tempting to ask if rather the impact of chemotherapy is greater on the RV than on the LV, but it is more plausible to interpret this as related to the higher value of the RVGLS compared to the LVGLS and probably to the larger percentage reduction in the RVGLS that may indicate cardiotoxicity. There has been very little focus on the cardiotoxicity of oncologic treatments, in general, on the right ventricle and almost none on the toxicity of antiangiogenic agents. Considering the thinner structure of the RV myocardium, with fewer myofibrils, the RV is probably also susceptible to the cardiotoxic effects of oncologic therapy. Although RV wall motion or functional abnormalities have been reported to occur during cancer therapy[15-19] and even at the time of cardiotoxicity[15], RV dysfunction is not considered in the diagnosis of cardiotoxicity and its incidence and prognostic value in this setting is unknown[15]. Our results build on the existing literature by demonstrating that right ventricular systolic function parameters are also reduced during antiangiogenic therapy, stressing that it is important to assess both ventricles during cancer therapy. In fact, the ASE Expert Consensus Statement on the multimodality imaging of adult patients receiving cancer therapy recommends to also monitoring RV function during cancer therapy[6]. Also, having in view the perspective of using angiogenesis inhibitors in the treatment of pulmonary artery hypertension, we believe that our results will inspire discussion.

Most of the antiangiogenic agents, such as sunitinib and sorafenib, have been purposefully designed to be "multi-targeting" and nonselective, blocking several tyrosine kinase receptors, with broader anticancer efficacy but an increased likelihood of toxicity[9]. This aspect makes it difficult to identify which targets mediate cardiotoxicity[9]. The mechanisms of myocardial toxicity induced by anti-VEGF agents should be regarded in relation to the "on-target" and "off-target" toxicities that these agents present[9]. "On-target" toxicity is when the intended targets of anti-VEGF agents are also implicated in normal cardiomyocyte survival, and thus their inhibition leads to myocardial dysfunction[9]. The "off-target" toxicity occurs when other kinases not intended to be targets of the agents are also inhibited[9]. In our study, there were no significant differences between the three types of antiangiogenic agents used (bevacizumab, sunitinib, and sorafenib) and the reductions in LVGLS, RVGLS, 2DLVEF, TAPSE or worsening/de novo HTN.

STUDY LIMITATIONS

The main study limitations were represented by the limited number of patients in our study, the relative rapid appearance of the cardiac toxicity (most of them at Visit 2), the high mortality and morbidity of oncologic patients receiving this medication (only 18 patients left at Visit 4) and the lack of a long-term follow-up. Due to that, there is a need for further studies in order to cover further gaps in knowledge as the possible predictive value of GLS reduction on the consequent reductions in LVEF or TAPSE; if the RV functional impairment was independent of or preceded a fall in LV function; if the reported cardiac toxicities are reversible or permanent.

CONCLUSIONS

Our results show the importance of an active cardiologic monitoring of oncologic patients receiving antiangiogenic therapy. We found that antiangiogenic therapy induces worsening pre-existing HTN or de novo HTN and also a reduction in all systolic function parameters of both ventricles in almost half of the studied patients. Also, myocardial dysfunction induced by antiangiogenic agents should not be regarded only as a consequence of HTN, but also as rather related to the intrinsic myocardial toxicity of these agents,

pre-existing HTN being probably a major permissive/ precipitating factor.

Conflict of interest: none declared.

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