REVIEW

CARDIOVASCULAR EFFECTS OF ANTIANGIOGENIC ONCOLOGICAL THERAPIES. THE FINE BALANCE OF BENEFITS AND RISKS

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Manuscript received: April 2015

Abstract

Agents targeting the vascular endothelial growth factor (VEGF) pathway have become broadly used in oncology and have significantly improved the management of certain solid malignancies, prolonging survival in cancers that were previously untreatable. Clinical studies reported cardiovascular toxicity associated with anti-VEGF agents (including arterial and venous thromboembolic events, QT prolongation, arterial hypertension and heart failure). The cardiovascular toxicity of these agents is unexplored in the "daily medical practice", in unselected patient populations. This review briefly presents the possible cardiac toxicity of these agents and their underlining mechanisms, as this is highly important both for the cardiologist and the oncologist in their effort to preserve the balance between the benefits and risks of this therapy. As accurate data on the actual incidence of the cardiotoxicity of these agents, especially of asymptomatic reduced left ventricular ejection fraction or overt heart failure remains yet unknown, there is a need for further studies to specifically investigate cardiotoxicity caused by anti-VEGF agents. Also, new strategies for early detection and prevention of cardiotoxicity from antineoplastic drugs are needed.

Rezumat

Agenții care vizează calea care implică factorul de creștere din endoteliul vascular (*VEGF*) au devenit larg utilizați în oncologie și au îmbunătățit în mod semnificativ tratamentul anumitor afecțiuni maligne precum și prelungirea supraviețuirii în cancere netratabile anterior. Studiile clinice au raportat toxicitate cardiovasculară asociată cu agenții anti-VEGF (inclusiv evenimente tromboembolice arteriale și venoase, prelungirea intervalului QT, hipertensiune arterială și insuficiență cardiacă). Toxicitatea cardiovasculară a acestor agenți este neexplorată în "practica medicală de zi cu zi", la populații neselectate de pacienți. Aceast studiu teoretic prezintă succint posibila toxicitate cardiacă a acestor agenți și mecanismele lor, subliniind că acest lucru este extrem de important atât pentru cardiolog cât și pentru oncolog în efortul lor de a păstra echilibrul între beneficiile și riscurile acestui tratament. Date cât mai exacte cu privire la incidența reală a cardiotoxicității acestor agenți, în special a reducerii asimptomatice a fracției de ejecție a ventriculului stâng sau insuficienței cardiace clinic manifeste, rămân încă necunoscute, fiind nevoie de studii suplimentare pentru a investiga în mod special cardiotoxicitatea cauzată de agenții anti-VEGF. De asemenea, sunt necesare noi strategii pentru detectarea precoce și prevenția cardiotoxicității terapiei antineoplazice.

Keywords: cardiotoxicity, angiogenesis, vascular endothelial growth factor (VEGF), anti-VEGF agents, thromboembolic events, QT prolongation, arterial hypertension, heart failure

Introduction

As the survival of oncologic patients has increased significantly in the last decades [1], the cardiotoxicity of chemotherapy has become an increasingly challenging issue. The reversibility of cardiotoxicity or the long-term cardiac safety of many antitumoural agents is still uncertain. Even molecular targeted therapies, first thought to have a safer profile than classic chemotherapy agents, are now associated with cardiac toxicities that require further investigation [2].

Angiogenesis represents the formation of new blood vessels from pre-existing ones. It is a critical determinant of cancer growth and metastasis and has become one of the primary targets of oncologic treatment [3, 4]. Angiogenesis is controlled by many growth factors, among which vascular endothelial growth factor (VEGF) plays the central role, promoting endothelial cell (EC) growth,

migration, and survival [5, 6]. Other angiogenic factors include fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF) and hepatocyte growth factor (HGF), and they all act in part by upregulating VEGF [7].

Agents targeting the VEGF pathway have become broadly used in oncology and have significantly improved the management of certain solid malignancies, prolonging survival in cancers that were previously untreatable. All of the anti-VEGF agents induce EC apoptosis (with vessel regression) and inhibition of EC proliferation (inhibiting angiogenesis). As, under physiological circumstances, more than 99% of endothelial cells are quiescent, and growth factor pathways are not activated, it was initially believed that anti-VEGF agents will act mostly on tumour-stimulated EC [8]. This perspective has changed as the VEGF signalling pathways were found to be crucial in the normal EC for maintaining homeostasis [8]. Clinical studies reported cardiovascular toxicity associated with anti-VEGF agents (including arterial and venous thromboembolic events, QT prolongation, arterial hypertension (HTN) and heart failure (HF)) at higher than anticipated rates [9, 10]. The cardiovascular toxicity of these agents is probably even more prevalent in the daily medical practice, in unselected patient populations [9, 10] as these agents are starting to be administrated on a long-term basis to patients who are increasingly older, with multiple comorbidities and as the survival of these patients continues to improve [7]. In this context, knowing the possible cardiac toxicities of these agents and understanding their underlining mechanisms becomes highly important both for the cardiologist and the oncologist in their effort to preserve the balance between the benefits and risks of this therapy.

The VEGF family

VEGF is produced by many cell types, including endothelial progenitor cells, EC, renal epithelial cells, fibroblasts, macrophages, and certain tumours [11, 12]. It is critical for EC survival, proliferation, migration and resistance to stresses; it inhibits apoptosis, increases vascular permeability and stimulates vasodilation *via* production of nitric oxide (NO) [11, 12]. Physiologically, it is implicated in angiogenesis during embryogenesis, wound healing, and menstruation. Pathologically, it is a critical determinant of tumour growth and metastases [5].

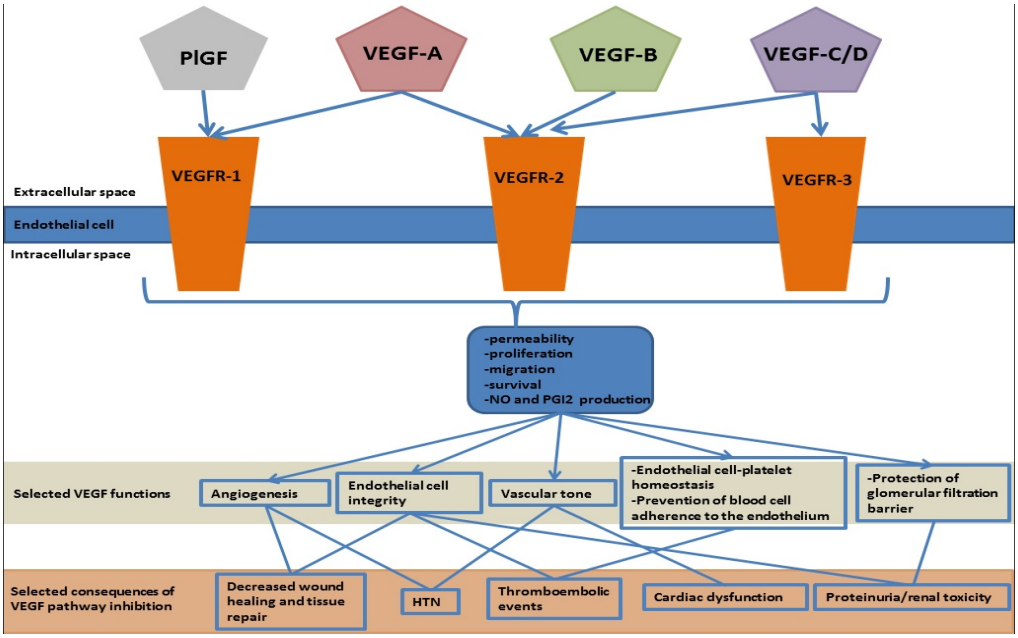

Figure 1.

VEGF action pathways and inhibition effects. Modified after [5] and [13]

PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; HTN, arterial hypertension.

In humans, the VEGF family comprises the following five isoforms: VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor (PlGF), and their receptors: VEGFR-1, -2, and -3 [11]. Among them, VEGF-A is the most biologically active and is produced by up to 60% of human cancers [11]. It binds to VEGFR-1 and -2, with VEGF-A binding to VEGFR-2 having the major biological effects [5, 11]. PlGF and VEGF-B bind to and activate only VEGFR-1. Although VEGFR-1

has a wider expression pattern compared with that of VEGFR-2 and can bind tightly to its ligands, it has a weak tyrosine kinase activity, generating signals weaker than VEGFR-2 [11, 14]. VEGF-C and -D have lymphangiogenic and to some extent angiogenic activities. They bind primarily VEGFR-3 on endothelial cells in lymphatic vessels and have a weak affinity for VEGFR-2 on blood vessels [11]. (Figure 1)

Anti-VEGF agents

So far, there are at least ten anti-VEGF agents (Table I) approved by the FDA (US Food and Drug Administration) to be used in oncology, with many more in development [5]. Among them, bevacizumab, sunitinib and sorafenib are the best known. Anti-VEGF agents target the VEGF pathway at various levels: the VEGF molecule, its receptors, or the downstream signalling pathways. They include monoclonal antibodies to VEGF (e.g., bevacizumab, ramucirumab) or soluble VEGF receptors (VEGF Trap) (e.g., Ziv-aflibercept), which bind and neutralize the VEGF molecule. Also, they include the small molecule tyrosine kinase inhibitors (TKI) that target VEGFR intracellular intrinsic kinase activity (e.g. sunitinib, sorafenib, vandetanib, axitinib, regorafenib, and pazopanib). TKI are not VEGFR-specific, as they also inhibit many other receptor tyrosine kinases [5].

Table I

FDA approved anti-VEGF agents, their mechanisms of action and selected indications [15]

Anti-VEGF agent	Mechanism of action	Selected indications by cancer type
Bevacizumab	Humanized anti-VEGF-A monoclonal antibody	-Metastatic *colorectal cancer* -Unresectable, locally advanced, recurrent or metastatic *non-squamous non-small cell lung cancer* -*Glioblastoma,*progressive disease following prior therapy -Metastatic *renal cell carcinoma* -*Cervical cancer* in persistent, recurrent, or metastatic disease. -Platinum-resistant recurrent *epithelial ovarian, fallopian tube or primary peritoneal cancer*
Sorafenib	Small molecule TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, c-kit receptor, intracellular RAF kinases (CRAF, BRAF, and mutant BRAF) and FLT3	-Unresectable *hepatocellular carcinoma* -Advanced *renal cell carcinoma* -Locally recurrent or metastatic, progressive, differentiated *thyroid carcinoma* refractory to radioactive iodine treatment
Sunitinib	Small molecule TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR α and β, c-Kit, FLT3, CSF1R and RET	-*Gastrointestinal stromal tumour* (GIST) after disease progression on or intolerance to imatinib mesylate. -Advanced *renal cell carcinoma*. -Progressive, well-differentiated *pancreatic neuroendocrine tumours* (pNET) in patients with unresectable locally advanced or metastatic disease.
Axitinib	Small molecule TKI of VEGFR-1, VEGFR-2, VEGFR-3	Advanced *renal cell carcinoma* after failure of one prior systemic therapy.
Vandetanib	Small molecule TKI of VEGFR, EGFR and RET	Late-stage (metastatic) *medullary thyroid cancer* in adult patients who are ineligible for surgery.
Ramucirumab	Human anti-VEGFR-2 monoclonal antibody	- Advanced or metastatic, *gastric or gastroesophageal junction adenocarcinoma* with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy
Zif-Alfibercept	Fusion protein that binds to VEGF-A, VEGF-B, and PlGF	- Metastatic *colorectal cancer* that is resistant to or has progressed following an oxaliplatin-containing regimen.
Regorafenib	Small molecule TKI of VEGFR-1, -2, -3, TIE2, PDGFR, FGFR, KIT, RET, RAF, BRAF, and BRAFV600E.	-Metastatic *colorectal cancer* who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. -Locally advanced, unresectable or metastatic *gastrointestinal stromal tumor* (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.
Pazopanib	Small molecule TKI of VEGF, PDGFR, FGFR and c-kit	-Advanced *renal cell carcinoma*. -Advanced *soft tissue sarcoma* who has received prior chemotherapy.
Cabozantinib	Small molecule TKI of c-Met and VEGFR2.	Progressive, metastatic *medullary thyroid cancer*.

The present paper will briefly review the existing data on the cardiac toxicity of the three best-known anti-VEGF agents: bevacizumab, sutinib and sorafenib. We mention the fact that the design of almost all of the existing studies on anti-VEGF therapy did not usually include the assessment of cardiac status, and only clinically significant cardiovascular events were recorded. Thus, the actual incidence of the cardiotoxicity of these agents, especially of asymptomatic reduced left ventricular ejection fraction (LVEF) or overt heart failure (HF) remains yet unknown and highlights the importance of further prospective studies with appropriate cardiovascular surveillance. Moreover, no data exist on isolated or coexisting right ventricular dysfunction associated with the use of these agents. Considering a preclinical study in which an anti-VEGF agent precipitated severe pulmonary arterial hypertension [16], it becomes evident that the right ventricle may also deserve further investigation in this setting [17].

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds VEGF-A, and prevents it from interacting with VEGFR-1 and VEGFR-2 [11]. Its indications for cancer type are described in Table I. All grade hypertension (HTN) has been reported in 22% to 36% of patients and severe HTN in 5.0% [2]. Hypertensive crises, sometimes leading to encephalopathy and subarachnoid haemorrhages have also been reported [2, 18]. It appears there is a direct relation between bevacizumab dose and HTN development [19, 20]. Other identified potential risk factors for bevacizumab-induced HTN are African American race and presence of renal cell carcinoma [21, 22]. HF was reported in up to 4% of patients, with a higher incidence in those pre-treated with anthracyclines or radiation to the mediastinum [2, 18]. Bevacizumab therapy has also been associated with an increased risk of thromboembolic events. In an analysis of five randomized trials, patients receiving bevacizumab presented a higher risk of angina pectoris, myocardial or cerebral ischemia/ infarct, or arterial thrombosis (3.8% *vs*. 1.7% in the control group; $p < 0.05$) [23]. Risk factors included older age, a history of previous arterial thrombotic events, and manifest arteriosclerotic disease [23]. There was no dose association, and cumulative exposure was not found to be a risk factor [23]. Data on bevacizumab or other anti-VEGF agents-induced venous thromboembolism are controversial. A meta-analysis of 15 randomized trials reported that bevacizumab therapy presented significantly higher risk for venous thromboembolism (RR 1.33; $p < 0.001$) [24]. Conversely, neither Scappaticci *et al.* nor Qi *et al.* found a significant increase in venous thromboembolism in their meta-analyses [23, 25].

In contrast to bevacizumab, the other anti-VEGF agents are multi-targeted TKIs. That means that besides growth factors or their receptors involved in angiogenesis, these agents also inhibit many other kinases involved in tumour cell proliferation. Thus, multi-targeted TKIs have a broader antitumoural activity, but also a higher potential to induce cardiotoxicity as many of the other inhibited kinases also have significant roles in maintaining the homeostasis of the cardiovascular system.

Sunitinib

Sunitinib is a multi-targeted TKI whose targets and indications are described in Table I. Sunitinib is administered orally and is metabolized predominantly by CYP3A4 in the liver [6].

In clinical trials, HTN of any grade induced by sunitinib was estimated at 15% up to 47% [2] of patients. Sunitinib appears to be associated with the highest risk of HF among anti-VEGF agents, but the reported incidence rates vary widely. Chu *et al.* reported that 28% of patients treated with sunitinib demonstrated an absolute reduction in LVEF of ≥ 10% and that 3 - 15% of patients presented overt HF [26]. In a recent clinical trial a total of 1% of patients treated with either pazopanib or sunitinib developed symptomatic HF, and another 9% of patients in each group demonstrated a ≥ 15% absolute decline in LVEF compared to baseline [27]. These results suggest that the incidence of asymptomatic LV dysfunction during treatment with sunitinib is probably higher than that of overt HF.

Other reported cardiovascular toxicities associated with sunitinib therapy include thrombotic events (2 - 3%) with myocardial ischemia in 1% of cases [17]. Sunitinib was also reported to induce bradycardia, PR interval prolongation and QT interval prolongation with torsades de pointes in less than 0.1% of sunitinib-treated patients [28].

Sorafenib

Sorafenib is a multi-targeted TKI that is administered orally and metabolized by the liver via CYP3A4 and UGT1A9 [6, 29]. Its mechanism of action and indications by cancer type are described in Table I. Reports indicate HTN of any grade in 9 - 17% of patients and HTN of grade 3 or more in 3 - 5% [11, 30]. In a recent meta-analysis, Li *et al.* report a higher rate of sorafenib induced HTN and of more serious HTN in patients with renal cell carcinoma than in those with other types of tumours [31]. The use of sorafenib was also associated with an increased risk of arterial thromboembolism [22], with cardiac ischemia/infarction being reported in ≤ 3% of cases [11, 30]. There are fewer data on the presence of HF in sorafenib treated patients. In an observational study, 14 out of 25 sorafenib treated patients (56%) had a cardiac event (abnormal cardiac enzymes, symptomatic arrhythmias requiring treatment, new LV systolic dysfunction, acute

coronary syndrome) and 3 of the 14 patients showed a decreased LVEF at the moment of the event [11, 30].

Other antiangiogenic agents have also been evaluated in a series of studies, but due to the limited number of patients it is yet difficult to draw conclusions on their cardiac safety.

Possible mechanisms and management of cardiovascular toxicity of anti-VEGF agents

The arterial hypertension (HTN)

HTN appears to be a frequent and dose-dependent adverse cardiac effect of all anti-VEGF agents [44]. In the trials, HTN was defined according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), as blood pressure (BP) higher than 150/100 or as a diastolic BP increase of more than 20 [6, 33]. These thresholds are higher than those in the HTN guidelines meaning that, probably, the real incidence of anti-VEGF induced HTN is even higher than reported so far [5]. An absolute increase in BP was observed in almost 100% of patients treated with anti-VEGF agents, reaching HTN thresholds in approximately 19% - 67% of patients [5, 35]. The highest magnitude of the increase in BP was reported to occur rapidly, within hours to days after the beginning of therapy with sustained BP increase by day 6 [5, 35]. Also, systolic BP seems to be affected more than the diastolic BP [5, 35]. Risk factors for anti-VEGF-induced HTN remain largely unknown. HTN was shown to be dose-dependent, with increasing incidence when multiple anti-VEGF agents were used in combination (e.g., bevacizumab and sunitinib) [5, 36]. Other reported risk factors include a previous history of HTN, age > 65 years, smoking, high BMI and hyper-cholesterolemia [5, 34, 37]. Withdrawal of the anti-VEGF agents was associated with a rapid decrease in BP [5].

Several mechanisms have been linked to the occurrence of VEGF inhibitor-related HTN (Table II).

Table II

Possible mechanisms of VEGF inhibitor-related HTN. Modified after [5] and [43]

Possible mechanism of anti-VEGF therapy-induced HTN	Pathophysiological effect
Microvascular rarefaction	Increased peripheral resistance
Decreased nitric oxide and prostacyclin production	Decreased vasodilatation Sodium retention
Reduced lymphangiogenesis	Reduced extracellular fluid buffering and volume overload
Neuroendocrine mechanisms Increased endothelin-1 levels	 Increased vasoconstriction
Increased arterial stiffness	Increased peripheral resistance
Renal dysfunction	Sodium retention ,volume overload

Microvascular rarefaction refers to a functional or structural decrease in the number of the small vessels of the microcirculation that can lead to increased systemic vascular resistance and HTN [10]. Steeghs *et al.* first demonstrated capillary rarefaction in patients treated with a VEGF inhibitor [6, 38]. Also, in a prospective study which showed a statistically significant elevation in the mean BP and a decline in the average dermal capillary density after six months of bevacizumab treatment, the degree of rarefaction correlated with the development of HTN, as well as with the total dose of bevacizumab [39]. However, there is still ambiguity regarding whether microvascular rare--faction is a cause or consequence of HTN. Also, uncertainty remains regarding whether capillary regression during VEGF inhibition encompasses all systemic vascular beds or is restricted to particularly vulnerable beds such as the thyroid, the trachea, the intestinal villi, and the skin [40]. Belcik *et al.* reported that neither reduced functional micro-vascular density nor significant alterations in arterial mechanical properties were primary causes of HTN during anti-VEGF therapy [41].

While VEGFR-2 activation leads to the up-regulation of eNOS (endothelial nitric oxide synthase) and production of the vasodilator prostacyclin (PGI2), inhibiting the VEGF pathway may lead to decreased nitric oxide and prostacyclin production [6, 10] resulting in an increased vascular resistance and HTN. An additional aspect regarding the impaired NO functioning and HTN may be related to its role in tubulo-glomerular feedback, pressure natriuresis, and sodium balance. Decreased levels of NO may lead to the development of HTN through sodium retention and direct renal effects [40, 42].

Some anti-VEGF agents (eg. sunitinib or sorafenib) also block VEGFR-3, thus reducing lymphangio-genesis. This leads to a decrease in the capacity of the lymphatic capillary network to form a compartment that buffers sodium and extracellular fluid volume and that can blunt the rise in blood pressure in response to a high salt diet [43].

Several neuroendocrine mechanisms were also investigated as potential contributors in the development of HTN, among which the role of an up-regulated renin–angiotensin–axis. However, Kappers *et al.* reported that sunitinib-induced increase in BP is accompanied by a decrease in renin and a considerable

rise in endothelin-1 levels [44]. Also, Veronese *et al.* assessed changes in plasma levels of endothelin-1, renin, aldosterone, urotensin II, and catecholamines in patients treated with sorafenib [45]. BP rose by 20 mm Hg in 60% of the patients but with no significant changes in the plasma levels of vasoactive mediators [45]. These results suggest that anti-VEGF induced HTN is not related to the renin-angiotensin or sympathetic nervous system.

In the same study Veronese *et al.* found that patients treated with sorafenib showed a significant increase in arterial stiffness, as suggested by the central aortic augmentation index and aortic pulse wave velocity [6, 45].

Interestingly, the occurrence of HTN can be regarded as a pharmacodynamic marker of anti-tumour response during anti-VEGF therapy [42]. Scartozzi *et al.* reported partial remission of the tumour in 75% of patients with bevacizumab-related HTN and in only 32% of those without HTN. Moreover, patients with grade II - III HTN, had a significantly longer progression-free survival than non-HTN patients [46]. Also, sorafenib treated patients with a longer progression-free survival (> 5 months) had higher grades of HTN compared to those with shorter disease-free survival [31, 47]. Also, when different anti-VEGF agents were compared, the ones with more frequent HTN also had longer progression-free survival [47, 48, 49]. Moreover, patients with certain VEGF genotypes were reported to have a better antitumor response, but also an increase in BP and possibly a decrease in LVEF [50]. Besides HTN, other additional toxicities were also correlated with the outcome, including myelotoxicity, hand–foot syndrome and fatigue/ asthenia [42].

The subject of toxicities as possible biomarkers of a successful outcome may raise the question of whether treating the toxicity would impair the outcome. In this context, studies show that treating HTN does not appear to alter the outcome. Moreover, in a retrospective analysis on HTN, as a predictive factor for outcome with sunitinib treatment, Szmit *et al.* reported that patients, which required at least three antihypertensive agents, had the longest progression-free survival [51]. In this context, dose-adjustment of anti-VEGF therapies according to toxicity was proposed as a way to improve tumour outcome. Maitland *et al.* inferred that dose titration as to produce an increase in BP may induce better antitumor effects and improve outcome of cancer patients [34]. The axitinib dose-titration trial showed that patients with dose titration, assessed by the occurrence of HTN, had a better outcome when compared to patients without dose titration [52]. More data is needed to validate these preliminary observations.

Weekly BP monitoring during the first cycle of anti-VEGF agents and then at least every 2 - 3 weeks for the entire duration of the anti-VEGF therapy, is recommended by the Cardiovascular Toxicities Panel of the NCI [34]. Anti-VEGF induced HTN is typically manageable with early initiation of antihypertensive agents to reach BP accepted targets [44]. If patients develop I HTN, antihypertensive treatment should be started, or previous antihypertensive therapy titrated [6, 11, 34] (Figure 2).

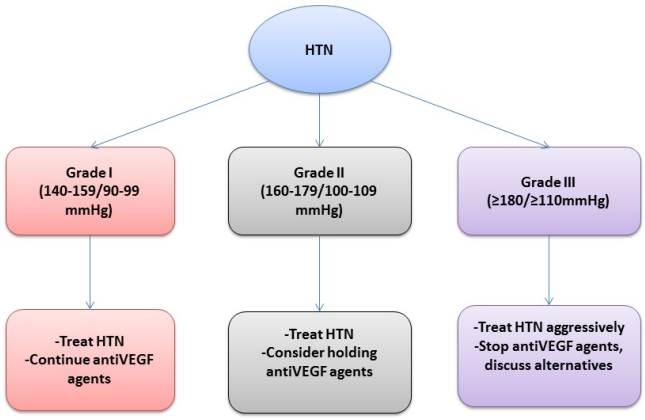

Figure 2.
Algorithm for the management of anti-VEGF induced HTN. Modified after [55]

There are no specific recommendations for the use of certain antihypertensive agents. Preferred agents include calcium channel blockers and ACE inhibitors, but there are very few data on the superiority of a single class of agents [6, 44]. ACE inhibitors were considered more efficient for many reasons: they may interfere with the NO pathway, prevent proteinuria and plasminogen activator inhibitor-1 expression, lower BP more rapidly than some dihydropyridine calcium channel blockers

and are also effective in preventing HF [6]. Still, in case of severe HTN, ACE inhibitors seem to have suboptimal BP-lowering effects [5], possibly because angiotensin II and renin levels are suppressed in patients with anti-VEGF-induced HTN [5]. Calcium channel blockers are particularly useful, perhaps because they reduce vascular smooth muscle cell contraction in vessels that are hypercontractile due impairment of NO and activation of ET-1 [5]. Amlodipine or nifedipine should be used, as nondihydropyridine calcium channel blockers inhibit the CYP3A4 isoenzyme and may increase sorafenib or sunitinib levels [6]. The use of beta-blockers is also encouraged, especially of beta-blockers with antioxidant properties due to their positive impact on cardiac mitochondria [6]. In some cases, anti-VEGF induced HTN is resistant to conventional antihypertensive drugs. Agents that directly interfere with VEGF targets, such as NO donors or ET-1 receptor blockers are being studied in this setting [5, 53, 54].

Left ventricular dysfunction and heart failure

Although clear data on the actual incidence lacks, the potential of anti-VEGF inhibitors to induce LV dysfunction is certain [17]. Anti-VEGF induced HTN may seem an obvious mechanism leading to LV dysfunction, but it is probably not the primary one, as neither the causality nor association between HTN and HF/ LV dysfunction was reported in any trial [56].

The mechanisms of HF-induced by anti-VEGF agents should be regarded in relation to the "on-target" and "off-target" toxicities that these agents present [7]. "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 [7]. The "off-target" toxicity occurs when other kinases, not intended to be targets of the agents, are also inhibited [7]. This is in relation with the non-selectivity of TKIs and to the fact that these agents were purposefully designed to be "multitargeting" agents, having a broader anticancer efficacy but an increased likelihood of toxicity [7].

VEGF was shown to be critical for capillary density in the myocardium and stem-cell differentiation into cardiomyocytes [10]. Preclinical studies in mice have well illustrated the risk of cardiotoxicity induced by inhibition of VEGF signalling. Cardio-myocyte-specific deletion of the VEGF gene in mice resulted in fewer coronary microvessels, thinned ventricular walls, and depressed contractile function [10, 57]. Preclinical studies have also shown that the role of VEGF signalling in the heart extends beyond angiogenesis and that it also mediates important compensatory responses to stress and injury [10, 58]. In animal models with hyper-trophied pressure-loaded hearts, VEGF reduced apoptosis and preserved contractile function by promotion of capillary growth [10, 59]. 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 [60]. Thus, inhibiting the VEGF pathway in the setting of HTN contributes to maladaptive hypertrophy of cardiomyocytes and possibly to LV dysfunction [61].

PDGF is another angiogenic factor targeted by anti-VEGF agents. PDGF signalling also plays a crucial role in the heart as absence of PDGFR-β in cardiomyocytes was shown to produce cardiac dysfunction and HF [62]. Sunitinib is the most potent inhibitor of the PDGF pathway, and it is probably not a coincidence that it presents the highest reported incidence of LV dysfunction and HF among the anti-VEGF agents. This high rate may also be related to the inhibition of "off-target" kinases. Inhibition of ribosomal S6 kinase (RSK) family by sunitinib leads to activation of the intrinsic apoptotic pathway and possibly to ATP depletion [11]. Also, inhibition of 5'-AMP-activated protein kinase (AMPK) worsens ATP depletion [11]. These effects result in energy compromise and cardiomyocyte dysfunction [11, 63]. A recent paper reported a direct dose-dependent negative inotropic effect of sunitinib on the myocardium, with a decline in intracellular Ca^{2+} and increased reactive oxygen species (ROS) generation [11, 64]. Endomyocardial biopsy in patients with HF after sunitinib treatment described the presence of cardiomyocyte hypertrophy and mitochondrial abnormalities but no necrosis, fibrosis or inflammation [11]. *In vitro* studies and in mice models showed that cardiomyocyte apoptosis was present only when sunitinib treated animals were also hypertensive [26]. Sorafenib also inhibits VEGF and PDGF pathways and other "off-target" kinases such as RAF-1 and BRAF kinases, which are essential for myocyte survival during stress conditions [63]. Cardiac deletion of RAF-1 induced dilation and reduced contractility, with increased myocyte apoptosis and fibrosis in rats [65].

An interesting aspect is that anti-VEGF agents have been reported to cause changes in the thyroid function. This may play a role in the development of cardiotoxicity as T3 has a direct effect on the cardiomyocytes, increases vascular resistance and induces endothelial dysfunction by reducing NO availability [42, 66, 67].

There is a need for further studies to specifically investigate cardiac dysfunction caused by anti-VEGF agents in detail. Having in view the data on cardiac dysfunction induced by trastuzumab and

anthracyclines, the role of traditional echocardiography with tissue velocity indexes and speckle tracking and real-time 3D echocardiography [68] should be pursued in future studies. The use of troponins and natriuretic peptides should also be further investigated in this setting [69].

Patients, who are receiving chemotherapeutic agents with potential cardiotoxicity, are considered patients at high risk of developing HF and should be closely monitored [11, 70]. Figure 3 presents a proposed algorithm for the management of patients with LV dysfunction induced by anti-VEGF agents. Symptomatic patients should be dealt with according to the HF guidelines, with ACE inhibitors and beta-blockers titrated to the highest tolerated doses, adding diuretics fluid retention [11, 55]. Future therapeutic perspectives include metformin, for the prevention of VEGF inhibitor–induced cardio-toxicity as it enhances AMPK activity [2, 71], and certain beta-blockers that enhance ERK activity, and that may be used for the treatment of sorafenib-induced cardiotoxicity [2, 72].

The reversibility of LV dysfunction and the resumption of VEGF inhibitors after improvement in EF are still uncertain issues. Schmidinger *et al.* reported 38 patients, who, after EF improvement, resumed TKIs in combination with cardiovascular protective drugs and did not show further relevant cardiac events [30]. By contrast, in another study, three patients had persistent cardiac dysfunction in spite of discontinuation of sunitinib and initiation of HF therapy [11, 73]. In a recent review Ewer *et al.* reported that that both symptomatic and asymptomatic adverse events (including LV dysfunction and HF) associated with sunitinib treatment were largely reversible, and that ongoing administration of anti-VEGF treatment in the presence of an event was not associated with fatal or life-threatening cardiac sequalea [74].

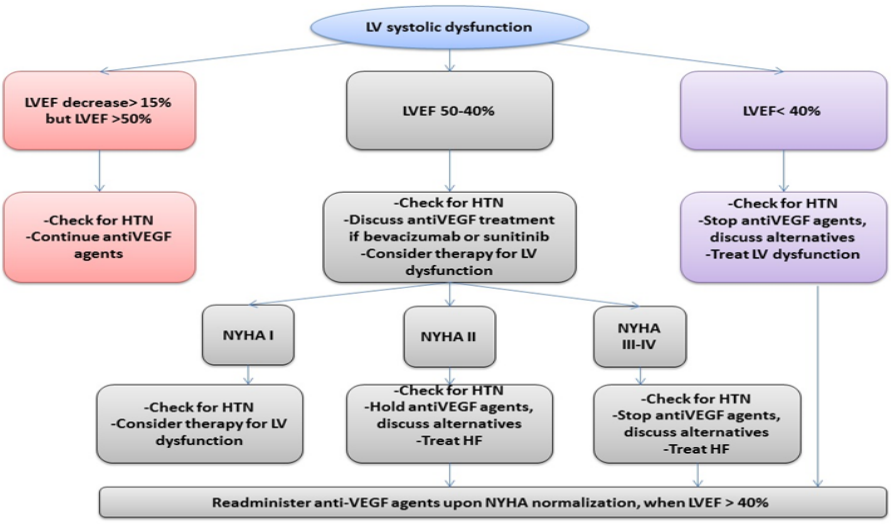

Figure 3.
Proposed algorithm for the management of LV dysfunction induced by anti-VEGF agents. Modified after [11, 55]

QT prolongation

Sunitinib, pazopanib [75] and especially vandetanib [76] therapy carry an increased risk of QT prolongation and torsades de pointes. It is recommended that in the presence of a history of QT prolongation, use of antiarrhythmic agents, bradycardia or electrolyte unbalances, sunitinib and pazopanib should be used with caution while vandetanib should be avoided. In patients receiving vandetanib, an ECG should be recorded at baseline, at 2 - 4 weeks, and at 8 - 12 weeks after the beginning of therapy, and then every three months [11, 75].

Thromboembolic events

As VEGF plays such an important role in the maintenance of vascular integrity, its inhibition has been related to both thrombosis and haemorrhage [10]. Abrogation of VEGF in EC increases apoptosis and alters the junctions between EC [10, 77], with subsequent exposure of the prothrombotic basement membrane, leading to aggregation and activation of platelets and also to the initiation of the coagulation cascade [10, 78]. Production of platelet inhibitors (prostaglandin I-2 and nitric oxide) is also inhibited by anti-VEGF agents [10, 78].

The use of antithrombotic agents, to attenuate the risk of arterial thromboembolism associated with anti-VEGF agents, is uncertain, and the increased risk of bleeding related to anti-VEGF agents should always be considered [79]. In a meta-analysis of bevacizumab trials, only 11% of the patients were treated with aspirin (ASA) prior to the arterial thromboembolic event and there was no significant association between the use of ASA and thrombosis [23].

Also, in patients who experience serious complications of thromboembolism, namely myocardial infarction or ischemic cerebrovascular events, a careful risks/ benefits analysis is needed prior to initiating antithrombotic treatment [79].

In the presence of asymptomatic ECG ischemic ST- and T-wave changes, interruption of anti-VEGF agent is recommended [75] and advanced cardiac testing is warranted. The decision to resume the anti-VEGF treatment with aggressive cardiologic support should be taken after a discussion between cardiologists and oncologists if the benefits of this treatment outweigh the cardiovascular risks [11, 75]. Angina or MI represents a strong indication for discontinuation of anti-VEGF therapies [11, 75].

Conclusions

Providing the maximum benefit of chemotherapy to an oncologic patient, while minimizing the inherent risk of cardiotoxicity associated with most of these agents, has become the great challenge of the cardio-oncology field. In order to balance decision-making between risks and benefits, a thorough understanding of cardiac risks associated with each agent is required. New strategies for early detection and prevention of cardiotoxicity from antineoplastic drugs are needed.

Acknowledgements

This paper is supported by the Sectorial Operational Programme Human Resources Developement (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390.

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