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Acute blood pressure elevation associated with biological therapies for cancer: a focus on VEGF signaling pathway inhibitors

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ABSTRACT

Introduction: Treatment with biological agents interfering with mechanisms of angiogenesis, such as vascular endothelial growth factor (VEGF) signaling pathway (VSP) inhibitors, was associated with an enhanced risk of acute and severe blood pressure (BP) increase and development of hypertensive emergencies.

Areas covered: The present article will review the scientific literature reporting hypertensive emergencies as a complication of biological treatment with VSP inhibitors. Hypertensive emergency is a life-threatening condition characterized by very high BP values (>180/110 mmHg) associated with acute organ damage. The exact mechanism of action is still incompletely clarified. Endothelial dysfunction following reduced bioavailability of nitric oxide has been hypothesized to play an important role in promoting hypertension and the occurrence of acute organ damage.

Expert opinion: Prevention, prompt recognition and treatment of hypertensive emergencies associated with treatment with VSP-inhibitors are essential to reduce the risk of adverse events. Not infrequently, the occurrence of hypertensive emergency led to VSP treatment discontinuation, with potential negative consequences on patient overall survival. The present review aims at providing detailed knowledge for the clinician regarding this specific issue, which could be of high impact in usual clinical practice, given the increasing burden of indications to treatment with biological agents targeted to the VEGF pathway.

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Arterial hypertension; hypertensive emergencies; cancer therapies; angiogenesis inhibitors; anti VEGF drugs; endothelial cells

1. Introduction

Hypertensive emergencies (HE) are defined as acute and severe blood pressure (BP) elevations with values of systolic BP over 180 mmHg and/or diastolic BP over 110 mmHg, associated with hypertension-mediated acute organ damage [1,2]. This definition includes a variety of heterogeneous clinical conditions, such as malignant hypertension, hypertensive encephalopathy, acute aortic disease, acute ischemic and hemorrhagic stroke, acute coronary disease, acute cardiogenic pulmonary edema and pre-eclampsia/eclampsia [3] (Table 1). Prompt recognition and immediate anti-hypertensive treatment is essential because if unrecognized and left untreated, many of these disorders may be life-threatening and associated with severe short-term adverse prognosis [4].

The development of biological treatment for cancer disease revolutionized the era of chemotherapy and dramatically ameliorated the life expectancy of patients affected by incurable forms of the neoplastic disease [5]. Moreover, the availability of targeted therapy was highly effective in reducing the toxicity related to traditional chemotherapy, although other unexpected and clinically relevant adverse events started to appear. One of the most frequent adverse cardiovascular effects of targeted therapy directed towards functional domains of the vascular endothelial growth factor (VEGF) signaling pathway (VSP) was the increased risk of hypertension development and severe BP increase. [6,7].

There are five sub-classes of VEGF, which cross-react with three families of tyrosine-kinase receptors (1, 2 and 3). VEGF-1 and VEGF-2 receptors have been found on the surface of endothelial cells; under physiological conditions, they regulate angiogenesis, lymphangiogenesis, and vascular permeability through the transduction of the signal by the activation of the receptor [8]. The inhibition of downstream signaling activated by VEGF-VEGF-receptor binding and the associated inhibition of angiogenesis have been hypothesized to represent the common pathophysiological pathway linked to BP increase. The clinical meaning of severe hypertension induced by treatment with VSP inhibitors as a marker of treatment efficacy and long-term better survival has been the object of extensive research. Whereas some studies showed a better prognosis for patients who developed treatment-induced hypertension [9–11], especially for those requiring multiple anti-hypertensive treatments [12], pooled results from other large-scale trials did not confirm this association [13,14], and this issue still remains controversial.

There is a consistent body of evidence showing that treatment with VSP inhibitors is associated with the

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Article highlights

- Treatment with biological agents interfering with mechanisms of angiogenesis, such as vascular endothelial growth factor (VEGF) signaling pathway (VSP) inhibitors, is associated with an enhanced risk of hypertensive emergencies.
- The possible link is represented by pharmacological inhibition of nitric oxide (NO) synthesis, impaired endothelium-mediated vasodilation, vasoconstriction, and microvascular damage
- Development of hypertension is the most frequent adverse event recorded in patients treated with VSP-inhibitors. Incidence of severe hypertension with associated organ damage is reported to be about 0.5–1.5%
- BP increases may constitute a life-threatening condition, when associated with acute hypertension-mediated organ damage such as malignant hypertension, acute kidney dysfunction, cardiac and cerebral ischemia, pulmonary edema, hypertensive encephalopathy, and acute aortic disease
- There is a knowledge gap about the prognosis of severe hypertension with associated organ damage induced by VSP-inhibitors. Systematic reporting in case series and clinical trials is mandatory in order to fill this gap in the future

This box summarizes key points contained in the article.

Table 1. Definition and clinical presentation of hypertensive emergencies associated with VSP-inhibitors.

Definition	Clinical presentation
Acute hypertensive microangiopathy	Coexistence of very high BP values (often >200/120 mmHg) with acute renal failure, proteinuria, ± advanced retinopathy and/or thrombotic microangiopathy.
Thrombotic microangiopathy	Severe BP elevation associated with Coombs-negative haemolysis and thrombocytopenia, in the absence of another plausible cause
Hypertensive encephalopathy	Severe hypertension and signs of cerebral impairment (seizures, lethargy, cortical blindness and coma), in the absence of an alternative explanation
Acute aortic disease	Acute aortic dissection, fissuration or rupture associated with very high BP values
Acute intracerebral disease	Acute ischaemic and hemorrhagic stroke
Acute cardiac disease	Severe hypertension associated with acute coronary syndrome (cardiac ischaemia or myocardial infarction), acute cardiogenic pulmonary edema, acute left ventricular systolic dysfunction

pharmacological inhibition of nitric oxide (NO) synthesis. This, in turn, determines reduced NO bioavailability, as confirmed by reduced concentration of NO metabolites such as nitrites [15] and impaired endothelium-mediated vasodilation [16]. Among the consequences of reduced NO bioavailability, the vasoconstriction related to the inhibition of NO production and the increase in proliferation of vascular smooth muscle cells density may constitute a potential pathophysiological link between treatment with VSP inhibitors and increased BP. This effect may contribute to prolong the duration of the hypertensive effect of VSP inhibitors over the long term [17]. Vasoconstriction and reduced NO availability could also be the pathophysiological mechanism linking treatment with VSP inhibitors to increased stiffness of central arteries, increased wave reflection and increased central BP as compared to peripheral BP, as suggested by some authors [18,19]. This may have important clinical consequences because central BP is more closely associated with hypertension-mediated organ damage than peripheral BP [20].

At the microvascular level, VSP inhibition was found to be associated with microvascular damage, expressed by reduced capillary density and both functional and structural capillary rarefaction [21]. Some studies also postulated the role of VSP inhibitors in inducing the synthesis of endothelin-1 (ET-1), a potent vasoconstrictor. This finding, although still recently under evaluation, could be promising given that endothelin-1 receptor blockers may reduce the vasoconstrictor effect of VSP inhibitors [22]. More recently, a functional link between VSP inhibition and interstitial free sodium retention has been postulated. It has been shown that interstitial sodium activates VEGF synthesis and subsequent lymphangiogenesis by macrophages, with the net effect of increasing sodium clearance [23].

Since the advent of Bevacizumab, the first recombinant, humanized, monoclonal antibody directed towards functional domains of VEGF-A that was approved in 2004 for the treatment of metastatic colorectal cancer, an increased risk of hypertension was clearly observed in subjects treated with this drug [24]. Ramucirumab, another fully human monoclonal antibody anti-VEGF receptor [25], and aflibercept, a VEGF decoy receptor [26], were also related to increased risk of hypertension. Finally, a number of other biological agents belonging to the family of small molecule protein tyrosine-kinase inhibitors (TKIs), such sorafenib, sunitinib, pazopanib, axitinib, lenvatinib, cediranib, vandetanib, lucitanib, lapatinib and regorafenib, have been also associated with treatment-induced BP elevation and related adverse consequences [27,28] (Table 2). These molecules are currently approved for the treatment of acute and chronic leukemias, gastrointestinal stromal tumors, and metastatic breast, liver and kidney cancer. Although characterized by a relatively short overall survival, patients treated with these drugs may, therefore, be subjected to the adverse effects of acute and severe BP increase that could represent, even in this particular clinical context, an important competing risk of death. The potential of these classes in inducing severe and life-threatening conditions associated with abrupt and severe increase in blood pressure, even in the early phases of drug treatment, remains relatively unexplored. Usually, the management of such situations requires drug discontinuation and prompt administration of anti-hypertensive treatment, often intravenously. However,

Table 2. Summary of the association between hypertension-mediated acute organ damage and main biological agents belonging to the family of VSP-inhibitors.

	Bevacizumab	Aflibercept	Sunitinib	Sorafenib	Pazopanib	Axitinib	Lenvatinib	Vandetanib	Cediranib	Regorafenib
Acute hypertensive microangiopathy	X	X	X	X	X				X	
Hypertensive encephalopathy	X	X	X	X	X	X	X	X	X	X
Acute aortic disease	X		X	X		X				
Acute intracerebral disease	X	X	X	X	X	X				
Acute cardiac disease	X	X	X	X	X	X	X			X

the majority of these drugs have long half-lives and the toxic effect may last longer than expected. Often, these events lead to permanent drug discontinuation, with an expected subsequent negative impact on overall prognosis.

The aim of the present review is to provide an overview of scientific evidence of the potential of VSP inhibitors in inducing hypertensive emergencies.

2. Severe BP increase associated with targeted therapy

The blood pressure increase is a relatively expected ancillary effect of anti-cancer treatment with VSP inhibitors, and virtually occurs in all patients. BP increase has been observed relatively early after initiation of treatment, and is usually reverted after treatment withdrawal. One of the first studies investigating the BP increasing effect associated with sunitinib, found that in more than 75% of treated patients there was an elevation in SBP, on average of 21 mmHg even after three months of treatment [29]. Other phase II and III trials and meta-analyses confirmed increased odds for hypertension in subjects undergoing treatment with VSP-inhibitors. Such risk was consistently found to be between four to six times higher as compared to routine care [7,30,31].

The class effect seems to be even stronger in newer VSP inhibitors, such as axitinib, lucitanib, and lenvatinib, which were associated with very high rates of hypertension incidence and acute adverse effects during treatment [32,33]. Reasons for such a higher risk may be related to different spectrum and specificity of target receptors. In fact, in the case of axitinib, the maximal inhibitory concentration against VEGF-receptor 1–3 was reported to be 10 times higher than sorafenib and sunitinib [34].

Studies reporting the incidence of hypertension according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), added very important information relative to the risk to develop hypertensive emergencies associated with the use of VSP inhibitors. According to the set of criteria used to classify and grade the severity of each adverse event occurring during cancer treatment, the development of hypertension during cancer treatment is considered as grade III hypertension if SBP was equal or higher than 160 mmHg or DBP equal to or higher than 100 mmHg, whereas hypertension associated with life-threatening consequences is graded as grade IV hypertension. Therefore, grade IV ideally correspond to the development of hypertensive emergency for which urgent treatment is indicated [35]. The majority of studies and meta-analyses, however, reported the development of high-grade hypertension, corresponding to grade III-IV hypertension. Only few studies separately indicated the incidence of grade IV hypertension.

In a cohort of 159 consecutive patients receiving targeted therapies with VSP inhibitors for metastatic renal cell carcinoma (92% receiving TKIs), hypertension was by far the most frequent adverse event recorded, accounting for about 40% of the total adverse events. The incidence of grade IV hypertension was reported to be about 2% (four cases). Of those, one patient was found among patients treated with sunitinib, one with sorafenib and two with pazopanib. It is unknown whether those patients were previously normotensive or had pre-existing hypertension [36]. In a meta-analysis of 20 randomized controlled prospective studies, for a total of 12.656 patients, the incidence of high-grade hypertension in patients receiving bevacizumab (n = 6.754) was 23.6%. In the subgroup of five studies (n = 2.771) separately reporting the incidence of grade IV hypertension, the incidence rate associated with treatment with bevacizumab was 0.5%. Based on these results, the relative risk for development grade IV hypertension associated with bevacizumab was 3.16 (95% CI:0.91–10.90; p = 0.069). Although not significant in this analysis, this result clearly suggests a trend towards an increased risk of developing hypertensive emergency associated with treatment with bevacizumab [37].

In a randomized phase III trial enrolling 1206 women with human epidermal growth factor receptor-2 (HER-2) negative operable breast cancer randomized to neoadjuvant plus adjuvant bevacizumab added to the neoadjuvant chemotherapy regimen, the incidence of grade 4 hypertension was reported to be 1% [38]. Other isolated cases of bevacizumab-induced grade IV hypertension were also found among 36 women with recurrent ovarian stromal tumors [39], among 57 patients with metastatic colorectal cancer [40], and among 26 patients treated for metastatic melanoma [41]. One case of grade IV hypertension with sunitinib was first reported in a preliminary study made on 15 patients with refractory acute myeloid leukemia [42]. Another case of grade IV hypertension was found among 22 patients with progressive metastatic renal cell carcinoma treated with sunitinib 50 mg once daily during an average follow-up period of 14.3 months [43].

In a review study conducted in subjects with metastatic renal cell carcinoma treated with sorafenib, one case of grade IV hypertension occurred among 32 patients treated [44]. In a phase III trial in which subjects with metastatic renal cell carcinoma were randomized to treatment with axitinib (n = 145) or sorafenib (n = 103), the incidence of grade IV hypertension was 1 case within each arm [45].

3. Hypertension-mediated acute organ damage

3.1. Acute hypertensive microangiopathy

Malignant hypertension is a rare condition, usually described as the coexistence of very high BP levels, acute renal failure, advanced retinopathy (such as retinal hemorrhages, cotton wool spots or papilledema) and/or thrombotic microangiopathy. Given the systemic nature of this condition, the name of the syndrome has been recently proposed to be changed in 'acute hypertensive microangiopathy' [1]. The acute phase of the disease is induced by the concomitant occurrence of endothelial dysfunction, pressure natriuresis and volume depletion which, in turn, result in ischemia of the renovascular microcirculation, acute renal failure, and activation of the renin-angiotensin-aldosterone (RAA) system. The subsequent BP increase induced by disproportionate RAA activation, with levels of plasma renin activity more than three times higher than normal, determines the basis of a vicious cycle. Manifestations of thrombotic microangiopathy, such as fibrinoid necrosis, hemolytic anemia, decreased platelet count,

increased lactate dehydrogenase (LDH) serum levels and presence of schistocytes, have often been described during the acute phase of malignant hypertension and highly correlate with the activation of the RAA system [46].

Endothelial dysfunction during treatment with VSP-inhibitors could, therefore, play a critical role in amplifying the risk of malignant hypertension and thrombotic microangiopathy in subjects predisposed, such as in subjects with uncontrolled hypertension. In such condition, the down-regulating effect of these drugs on the RAA system, which was observed in other clinical contexts [22], may not be sufficient to counterbalance the dramatic increase in the concentration of serum renin levels. However, the exact causal relationship between treatment with VSP inhibitors, induction of severe hypertension and the development of features associated with microangiopathy remains to be fully elucidated. Several studies suggested that renal lesions induced by VSP inhibition, such as proteinuria, kidney injury and thrombotic microangiopathy are related to direct VEGF disruption at the glomerular level. Paracrine signaling of VEGF is, in fact, essential in maintaining the integrity of the glomerular filtration barrier. The interaction between VEGF produced by podocytes and VEGF-2 receptor on the endothelial surface of glomerular cells is important to preserve the normal integrity of the filtration barrier. One study demonstrated that in mice with inhibition of the VEGF-A gene at the level of podocytes, overt proteinuria, and nephrotic syndrome occurred as the result of podocyte foot depletion and increased endothelial fenestrations [47].

In humans, the inhibition of VSP signaling results in proteinuria, nephrotic syndrome and thrombotic microangiopathy [48]. Although overt proteinuria was found very early after initiating treatment, structural features of kidney damage, such as glomerulosclerosis, mesangiolysis and membrane disruption, were observed only after long-term treatment [49]. Interestingly, glomerular and tubular lesions associated with treatment with VSP inhibitors, including thrombotic microangiopathy, were substantially similar to those found as the long-term sequelae of uncontrolled hypertension. However, there are no sufficient data showing a possible relationship between increased blood pressure and the occurrence of kidney damage under VSP inhibitors treatment. It is even more intriguing the evidence that features of drug-induced kidney damage are similar to those observed during preeclampsia. In this case, in fact, the excess of soluble form of anti-angiogenetic factor Flt-1 plays a key role in reducing circulating levels of placental growth factor (PlGF) and VEGF, mimicking the effect of anti-VEGF drugs [50].

Clinical studies and meta-analyses of randomized controlled prospective trials seem to support the hypothesis that the presence of increased BP could have a role in amplifying the microvascular damage affecting the kidney and systemic vasculature during treatment with VSP inhibitors. A retrospective analysis of pooled clinical data from phase III studies, conducted on 1392 patients with metastatic renal cell carcinoma treated with VSP inhibitors (pazopanib and sunitinib), showed that proteinuria developed early after treatment initiation (on average 32 days), and that hypertension was a significant risk factor for the development of proteinuria (HR per 10 mmHg increase 1.14, 95%CI 1.02–1.28) [51]. Tumor type (especially renal cell carcinoma), the presence of monolateral nephrectomy and drug dosage have also been involved as potential effect modifiers in the cascade of the events linking targeted therapy with hypertension and proteinuria [52].

3.2. Hypertensive encephalopathy

Hypertensive encephalopathy, on its classical clinical manifestation of posterior reversible encephalopathy syndrome (PRES), is another typical clinical feature associated with severe and abrupt BP increase. PRES is characterized by the occurrence of clinical symptoms including encephalopathy, seizure, headache, visual disturbance, focal neurological deficit and epilepsy [53]. Although reversible by prompt and appropriate treatment with anti-hypertensive drugs, the clinical picture may be complicated by the occurrence of irreversible and life-threatening complications such as secondary cerebral ischemia or bleeding [54]. The diagnosis is made by instrumental neuroimaging, usually brain MRI, showing the presence of bilateral white matter abnormalities typically in the posterior regions of the brain. The pathophysiology involves endothelial dysfunction following abrupt BP increase or provoked by toxic effects of cytokines on the endothelium. This lead to the breakdown of blood-brain barrier (BBB), lost of the auto-regulatory capacity and brain edema [55]. In the cascade of events induced by systemic BP increase, leading to arteriolar vasoconstriction as a response to increase in transmural pressure, the integrity of the so-called neurovascular unit, comprised of neuronal, endothelial, and glial components of the BBB, is essential. In fact, endothelial cells of the blood-brain barrier act as sensors of increased transmural pressure, being subjected to pressure-induced cytoskeletal deformations, and transducing the signal to smooth muscle cells in order to increase vascular tone [56].

Targeted treatment with VSP inhibitors could negatively influence the cascade of pathophysiological events leading to hypertensive encephalopathy. As occurs at the renal level, the critical role of the endothelium of the BBB may be impaired by concomitant targeted treatment. At the physiological level, VEGF has a fundamental role in vascular remodeling and angiogenesis by regulating the migration, proliferation, and survival of endothelial cells at the level of the BBB [57]. When exogenously administered, increased levels of VEGF were associated with enhanced permeability of the BBB leading to vasogenic edema [58]. This occurs also in the presence of other pathological conditions such as brain injury [59]. On the opposite, when VEGF levels were increased under physiological conditions, such as during pregnancy, the integrity of the BBB is usually preserved [60]. Even if, at least theoretically, VSP-inhibitors may contribute to decrease the risk of vasogenic edema, endothelial dysfunction and decreased NO bioavailability associated with treatment with anti-VEGF drugs may increase the risk of BBB dysfunction and breakdown through VEGF-independent pathways [61]. Taken together, these data suggest that endothelial dysfunction induced by treatment with VSP-inhibitors plays a pivotal role in enhancing the risk of hypertensive encephalopathy associated with severe hypertension.

The potential causative role of bevacizumab in the development of PRES was hypothesized for the first time by Glusker *et al* and Ozcan *et al* [62] in 2005, in subjects affected by renal and rectal cancers, respectively. An increasing number of clinical cases, relatively to the occurrence of PRES during treatment with VEGF-inhibitors, have been subsequently described in recent literature. Other cases were associated with treatment with sorafenib, sunitinib, pazopanib, and regorafenib. The overall incidence of PRES was reported to be about 0.5% [63].

A comprehensive review of reports documenting the occurrence of PRES during treatment with VSP inhibitors previously attempted to better characterize individuals at higher risk. The majority of the cases regarded subjects treated with bevacizumab, the first commercially available humanized monoclonal antibody against VEGF. The majority of the patients were females (73.1%), and received treatment in combination with chemotherapy (86.7%). The median duration of the treatment was 9.5 weeks. Most (92.3%) but not all the patients had hypertension at the time of diagnosis of PRES, whereas only a third had a past history of hypertension before starting treatment. The most frequent clinical features of PRES were headaches, visual disturbances, and seizures. The median time of neurological recovery was 8.9 days. In all the patients, the occurrence of PRES led to drug discontinuation; in selected cases, especially when alternative treatment was limited, drug reintroduction was attempted along with close BP monitoring and aggressive management of BP increase [64]. In one case, PRES was diagnosed in a patient early treated with regorafenib (4 days), after that bevacizumab was discontinued few months before, suggesting that previous treatment with VSP inhibitors may be a risk factor [39]. After permanent drug discontinuation, the long-term prognosis seems to be unaffected. However, in some cases, PRES occurrence was associated with adverse outcome [65].

Although severe hypertension is clearly involved in the etiopathogenesis of PRES associated with treatment with VEGF-inhibitors, some authors suggested that this may occur even in patients with normal BP values at the time of diagnosis. A case of a patient with concomitant occurrence of nephrotic syndrome and signs of cerebral edema occurring 7 days after treatment initiation with pazopanib was also described [66]. Two cases of PRES among patients treated with lenvatinib for radioactive iodine-refractory differentiated thyroid and anaplastic thyroid disease were also reported [23,67]. Even in this case, given that drug concentration may remain active in the body for more than 7 days, the expected effects of treatment withdrawal on BP increase and PRES regression may last longer than expected.

3.3. Acute aortic disease

Type A acute aortic dissection is a life-threatening medical emergency associated with very high short-term mortality. When associated with abrupt and severe BP increase, it is defined as a hypertensive emergency. In acute aortic disease, BP lowering should be rapidly pursued in order to reduce the progressive involvement of other areas of dissection.

Although not systematically assessed, there is an increased risk of aortic dissection in subjects undergoing anti-VSP targeted treatment for cancer associated with BP increases. The first case report described a 70 years old patient treated with a chemotherapeutic regimen including bevacizumab for metastatic prostate cancer. Such a patient had a long-lasting history of controlled hypertension, and he developed severe uncontrolled hypertension after 10 months after starting treatment with bevacizumab. Together with elevated BP levels (180/70 mmHg), the patient presented right shoulder pain and shortness of breath and a diagnosis of acute descending aortic dissection was made. The patient was promptly treated with intravenous anti-hypertensive medications and bevacizumab was withdrawn [68]. Acute dissection of the descending aorta was also found in a previously normotensive 77-year-old female patient after three months of treatment with sorafenib during a phase II trial for the treatment of renal carcinoma, in combination with gemcitabine and capecitabine [69]. One case of aortic dissection was also described in a phase-II trial reporting the efficacy of combination treatment of gemcitabine, capecitabine, and bevacizumab for metastatic urothelial cancer [70]. The Japanese Adverse Drug Event Report database reported an overall prevalence rate of aortic dissection in subjects treated with VSP inhibitors by 0.3%, with a median onset time of 105 days. The odds ratio to develop aortic dissection in the group of subjects treated with VSP-inhibitors as compared to untreated subjects was 22.3 (95%CI 11.2–49.4) [71].

Interestingly, as in the case of PRES, aortic dissection was found in subjects treated with TKIs also in the presence of controlled BP. In a 48 years old patient treated with sunitinib for renal cell carcinoma, who previously withdrew pazopanib and lapatinib for overt proteinuria, the development of acute Stamford type A aortic dissection with massive cardiac effusion occurred in the presence of controlled hypertension [72]. In another clinical case report, Stamford type A aortic dissection was found in a 66 years old patient first treated with sorafenib and subsequently switched to axitinib for liver cancer, after that hypertension control was obtained by anti-hypertensive treatment. In this patient, aortic dissection developed in conjunction with proteinuria and cardiac systolic dysfunction [73].

These evidences raised the hypothesis that the pathophysiology of aortic damage may be related to factors other than BP increase. In fact, the role of VEGF in the development of aortic aneurysm is rather controversial. At the experimental level, the increased angiogenesis induced by overexpression of VEGF, resulting in an increased rate of thoracic and abdominal aortic aneurysm formation, whereas its inhibition was associated with a reduction of its development [74,75], thus suggesting a potential role of VSP inhibitors in preventing the development of aortic dissection. However, in other animal models, the intracellular pathway activated by the binding between VEGF and VEGF-R promotes the expression of AKT which, in turn, play a role in determining a positive balance between matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 (MMP-9/TIMP-1). This impaired balance in favor of MMP-9 may be responsible for abnormal elastic fibers and aortic dissection after experimentally induced hypertension, as observed in AKT knock-out mice [76]. Interactions of VSP inhibitors with transforming growth factor beta (TGF-β) signaling could be another pathway involved in the pathogenesis of aortic aneurysms [77]. Interestingly, changes in the vascular structure mediated by VSP inhibitors may be responsible for the BP-

independent increase in arterial stiffness, as observed in human studies [78].

3.4. Acute intracerebral disease

Long-term hypertension is a well-acknowledged marker of risk for acute ischemic and hemorrhagic stroke. However, acute cerebrovascular events can also occur during acute BP elevations or after major stress [79], especially for hemorrhagic stroke [80]. Moreover, the degree of BP increase during the acute phase of ischemic and hemorrhagic stroke are closely related to early mortality [81]. For such reason, these events are listed as hypertensive emergencies [1]. The risk of acute ischemic and hemorrhagic stroke associated with the use of VSP inhibitors has been a matter of long debate. Previous case series suggested an increased risk of cerebrovascular events [82,83], although important findings relative to the mechanism involved (small vessel disease, cardio-embolic stroke), positive history of hypertension, concomitant disease and medication (especially those increasing bleeding risk) were commonly unreported. As expected, both ischemic and hemorrhagic stroke are significantly increased in brain tumors. In a phase II study of bevacizumab plus irinotecan in children with recurrent malignant glioma and intrinsic brainstem glioma, 19% of enrolled patients (6 out of 32: 4 hemorrhagic, 2 ischemic) developed cerebrovascular events potentially related to treatment with bevacizumab.

In a meta-analysis of 17 RCTs conducted with bevacizumab, the risk of acute cerebrovascular events was found to be significantly elevated with respect to controls, with a relative risk of 3.22 for ischemic events (95% CI, 1.71–6.07) and 3.09 for hemorrhagic events (95% CI, 1.36–6.99). Sub-analyses demonstrated that the risk increased at increasing dosage and in subjects with metastatic colorectal cancer [84]. The incidence of hemorrhagic stroke was also reported to be between 0% and 3% in trials performed with TKIs, and in the majority of the cases, they were fatal [85]. In a report of the Surveillance, Epidemiology, and End Results-Medicare database, the use of sunitinib and sorafenib in the treatment of advanced renal cell carcinoma was associated with a significantly increased risk for stroke (hazard ratio 2.84, CI 1.52–5.31), especially among older subjects [86].

In a trial evaluating the effectiveness of treatment with ponatinib in patients with chronic myeloid leukemia not responsive to first- and second-line TKIs, an evidence of increased BP was found in 67% of the patients enrolled. The rate of cerebrovascular events after two years of treatment was 7% [87].

3.5. Acute cardiac disease

Treatment with VSP-inhibitors is associated with various forms of cardiac diseases, such as heart failure, pulmonary edema, stable angina, and acute coronary syndrome, in which abrupt and severe BP increase induced by treatment may play a concausal role.

Experimental studies conducted in mice with deletion of genes codifying for VEGF synthesis showed myocardial capillary rarefaction and reduced contractile response to inotropic agents [88]. Endothelial autocrine and paracrine VEGF signaling is supposed to play an essential role in the stability of the cardiac microvasculature and myocardial function. VEGF also regulates survival and function of endothelial cells, and selective deletion of endothelial-derived VEGF synthesis leads to increased apoptosis, platelet activation, and formation of intravascular micro-thrombosis [89]. Interestingly, in models of diabetic cardiomyopathy, where VEGF synthesis is downregulated [90], and peripartum cardiomyopathy, characterized by an excess of VEGF inhibitors such as soluble FMs-like tyrosine kinase 1, the same phenotype of endothelial dysfunction, microvascular rarefaction and impairment of myocardial contractility were similarly observed [91].

Asymptomatic left ventricular dysfunction and clinically overt heart failure have been associated with sunitinib in randomized controlled trials [92]. Pre-existing hypertension and coronary artery disease were found as two main risk factors for cardiac toxicity and the development of heart failure [93]. The overall prevalence of heart failure was estimated to be included between 1% and 4% [94], and in many cases, cardiac heart failure was the main reason for death. Unfortunately, inconsistencies in data reporting generated several concerns related to the classification of cardiac adverse events [95].

The risk of acute coronary syndrome under treatment with bevacizumab is more than doubled with respect to the general population [96]. The risk seems to be even higher in subjects treated with TKIs, such as sunitinib, pazopanib, sorafenib, and ponatinib. Interestingly, often cardiac ischemic damage related to TKIs has atypical pathophysiology. It is not related to classical plaque fissuration and rupture, but mainly from result plaque obliteration, hyper-aggregation and spontaneous coronary artery dissection [97]. Moreover, ACS presentation could develop at any point of the treatment period, and in some cases even after a month [98]. Tako tsubo cardiomyopathy was also reported to be associated with the use of some VSP inhibitors, such as sunitinib, axitinib, and bevacizumab. An important role in determining abnormal coronary vasoreactivity leading to tako tsubo cardiomyopathy in subjects treated was related to pericyte dysfunction.

4. Treatment of hypertensive emergencies associated with targeted therapy

As for other acute hypertension-mediated organ damages, treatment of hypertensive emergencies occurring during treatment with VEGF-targeted therapy is driven by the type of organ involvement. The treatment goal itself is disease-oriented, and in the majority of the cases requires intravenous administration of drugs and close hemodynamic monitoring [1].

An important issue on this specific clinical scenario is related to the decision of how and when withdraw or reduce the dosage of the anti-angiogenetic medication which causes or contributes to raise BP levels. According to the Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee, the presence of hypertensive emergency is a clinical condition in which drug withdrawal should be considered [99]. However, it should be taken into account that the contribution of VSP-inhibitors to BP increase may last longer than expected after drug

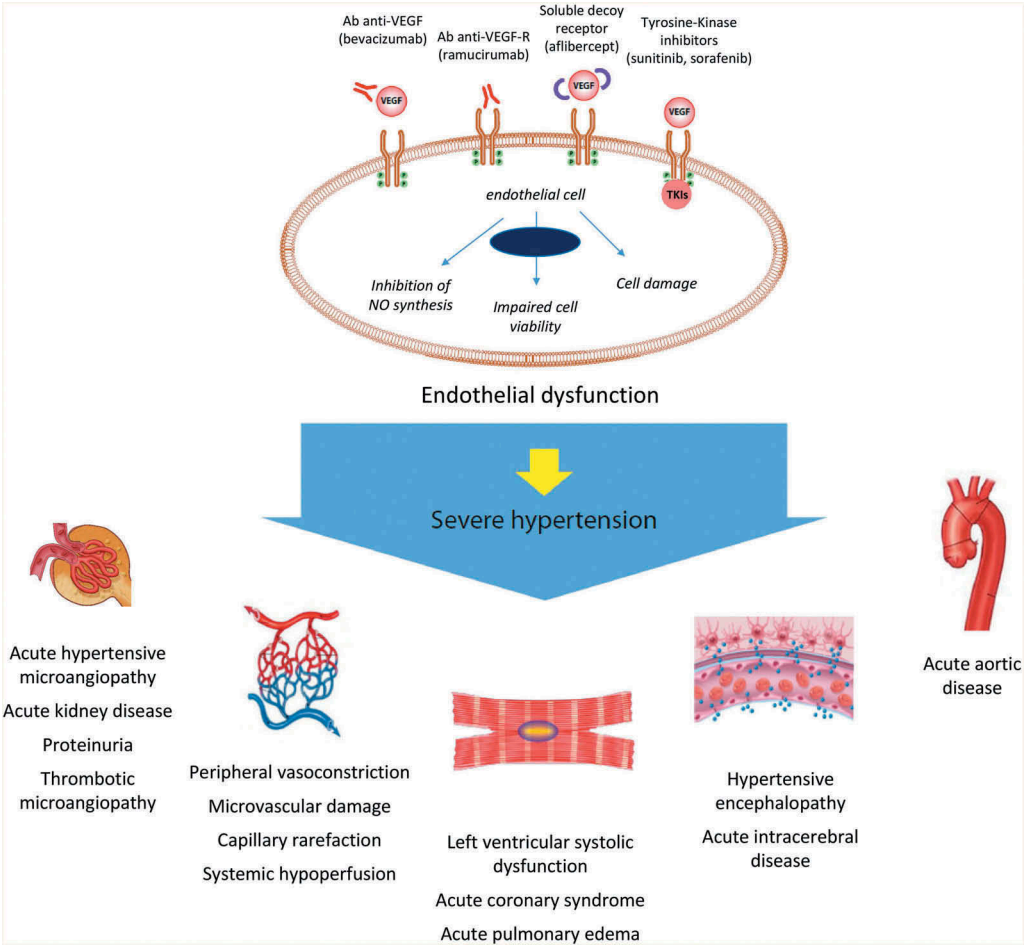

Figure 1. cascade of events and mechanisms linking endotelial cell dysfunction to severe hypertension and development of hypertensive-mediated acute organ damage.

withdrawal, because of the high specificity with receptors and long half-lives [34]. Therefore, in any case, treatment with intravenous anti-hypertensive drugs should be delayed on the basis of the expected BP reduction after VSP-inhibitors withdrawal. For the same reason, treatment shift of VEGF-inhibitors or TKIs to another drug of the same class should be performed with extreme caution and always after consulting with an oncologist. In fact, the evidence of the occurrence of a hypertensive emergency subsequently to a treatment shift was not infrequent in case reports [72,73].

To the best of our knowledge, there is no evidence available from randomized clinical trials suggesting the effectiveness of specific anti-hypertensive drug classes for the treatment of VSP inhibitors-induced hypertensive emergencies. Although at least theoretically, the development of hypertension under treatment with VSP-inhibitors may be considered the consequence of reduced NO availability, there is no scientific evidence supporting the choice to prefer NO donors, such as nitroglycerin or sodium nitroprusside, to other intravenous anti-hypertensive drugs. Calcium-channel blockers, such as nicardipine or clevidipine, or beta-blockers with associated anti-alpha$_1$ activity, such as labetalol, may also be considered as alternative treatments. As in the case of anti-hypertensive long-term oral treatment, non-dihydropyridine calcium-channel blockers, such as verapamil and diltiazem, should be avoided in patients receiving VSP-inhibitors, because of the competitive binding to the cytochrome P450 3A4 [100].

5. Expert opinion

The development of hypertension was the most frequent adverse event observed in subjects undergoing medical treatment for cancer. Anti-angiogenetic drugs targeted to the inhibition of VSP signaling have been demonstrated to be effective in ameliorating the overall survival of patients affected by different tumor types. These drugs have been consistently associated with an increased risk of early development of hypertension and severe BP increase. Such risk seems to be four to six times higher than controls. In rare cases, BP increases associated with the use of VSP-inhibitors were high enough to constitute a life-threatening condition, because it is known that acute and severe BP increases may be responsible for hypertensive emergencies characterized by acute organ damage such as malignant hypertension, acute kidney dysfunction, cardiac and cerebral ischemia, pulmonary edema, hypertensive encephalopathy and acute aortic disease (Figure 1).

The prevalence of hypertensive emergencies among subjects treated with VSP-inhibitors was reported to be approximately 0.5%. If not adequately diagnosed and treated, these conditions are associated with a very high risk of adverse outcome. Therefore prompt recognition, drug withdrawal and appropriate treatment of hypertensive emergencies are mandatory to reduce such risk and increase the overall survival. Endothelial dysfunction associated with impaired paracrine VEGF signaling is an important cornerstone of microvascular damage leading to acute organ dysfunction, even though many mechanisms remain to be fully elucidated.

There is a need for a better awareness of the potential clinical implications of acute and severe BP increases associated with the use of VSP-inhibitors, and the related prognostic meaning. Underestimation of the overall risk, low awareness of the importance of close BP monitoring and inconsistencies in adverse event reporting in clinical trials, still represent important limiting factors in risk prediction, prevention, prompt diagnosis and appropriate management of hypertensive emergencies in patients treated with VSP-inhibitors for cancer disease.

Currently, the potential causative association between treatment with VSP-inhibitors and development of hypertensive emergencies is critically biased by underreporting. There is a need, in the future, to overcome this limitation by systematically checking and reporting, in clinical trials and case series, for the association between the occurrence of organ damage potentially linked to acute BP increase and the administration of VSP-inhibitors. Details of hypertension history, changes in anti-hypertensive treatment, and the number of patients showing acute and severe BP increase, along with the number of hypertensive emergencies, should be better characterized. Moreover, the outcome of patients who are affected by organ damage potentially related to severe hypertension should also be systematically reported, as well as the BP response to urgent treatment and any adverse event following drug withdrawal. To our opinion, this is mandatory in order to improve the prognosis and clinical outcome of patients undergoing treatment with VSP-inhibitors.

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