Redox Biology 6 (2015) 421–425

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Research Paper

Treatment of sunitinib-induced hypertension in solid tumor by nitric oxide donors ☆

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ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form
8 September 2015
Accepted 9 September 2015
Available online 10 September 2015

Keywords:
Tyrosine kinase inhibitors
Hypertension
Vascular endothelial growth factor
Nitric oxide
Renal cell carcinoma
Sunitinib

ABSTRACT

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are overexpressed in the majority of renal cell carcinomas. This characteristic has supported the rationale of targeting VEGF-driven tumour vascularization, especially in clear cell RCC. VEGF-inhibiting strategies include the use of tyrosine kinase inhibitors (sunitinib, axitinib, pazopanib, and sorafenib) and neutralizing antibodies such as bevacizumab.

Hypertension (HTN) is one of the most common adverse effects of angiogenesis inhibitors. HTN observed in clinical trials appears to correlate with the potency of VEGF kinase inhibitor against VEGFR-2: agents with higher potency are associated with a higher incidence of HTN. Although the exact mechanism by tyrosine kinase inhibitors induce HTN has not yet been completely clarified, two key hypotheses have been postulated. First, some studies have pointed to a VEGF inhibitors-induced decrease in nitric oxide synthase (NOS) and nitric oxide (NO) production, that can result in vasoconstriction and increased blood pressure. VEGF, mediated by PI3K/Akt and MAPK pathway, upregulates the endothelial nitric oxide synthase enzyme leading to up-regulation of NO production. So inhibition of signaling through the VEGF pathway would lead to a decrease in NO production, resulting in an increase in vascular resistance and blood pressure. Secondly a decrease in the number of microvascular endothelial cells and subsequent depletion of normal microvessel density (rarefaction) occurs upon VEGF signaling inhibition.

NO donors could be successfully used not only for the treatment of developed angiogenesis-inhibitor-induced hypertension but also for preventive effects.

1. Introduction

Every year more than 270,000 new cases of kidney cancer are diagnosed worldwide in Europe 40% of patients with renal cancer die from this disease. Surgery is the treatment of choice in patients with tumors limited to the kidney, whereas in metastatic disease systemic therapy is often used.

The Von Hippel Lindau (VHL) protein plays a central role in the pathogenesis of clear cell renal carcinoma [1]. In a normoxic state, pVHL allows degradation of HIF. HIF-alpha is responsible for inducing expression of genes associated with angiogenesis and proliferation, such as vascular endothelial growth factor receptor (VEGF), platelet-derived growth factor receptors (PDGF), and TGF-alpha. While HIF is mostly active in hypoxic conditions, VHL defective renal carcinoma shows constitutive activation of HIF even in oxygenated environments. Intracellular accumulation of HIF-alpha stimulates the transcription of genes regulating VEGF, PDGF and TGF-alpha.

For many years inmunotherapy with high dose IL-2 was the only treatment used in this disease. However efficacy of this agent is low, with important toxicity associated although complete responses could be obtained in some patients. In the last years tyrosine kinase inhibitors (TKI), mTOR inhibitors, new inmunotherapy agents and other drugs have changed the choices available for use.

Anti VEGF and antiVEGFR agents are effective mainly in clear cell renal carcinoma because VEGF is elevated in the majority of these tumors. Hypertension (HTN) is commonly associated with angiogenesis inhibitors that target the VEGF pathway and appears to be a generalized effect of this class of agents, including sunitinib, axitinib, pazopanib, sorafenib and bevacizumab, which are

Abbreviations: NO, nitric oxide; NOS, nitric oxide synthase; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor; RCC, clear cell carcioma; TKI, tyrosine kinase inhibitors

☆This article belongs to a special issue on Nitric Oxide and Cancer, edited by Jordi Muntané and Benjamin Bonavida.

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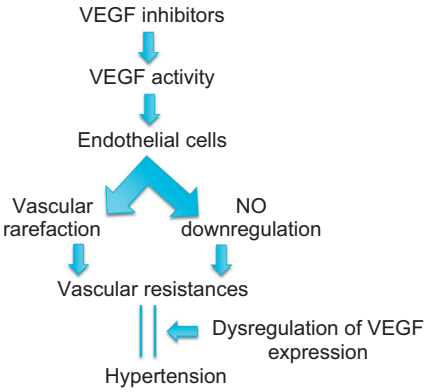
http://dx.doi.org/10.1016/j.redox.2015.09.007



VEGF: vascular endothelial growth factor; NO: nitric oxide. HTN: hypertension.

Fig. 1. Hypertension induced by VEGF inhibitors. VEGF: vascular endothelial growth factor; NO: nitric oxide. HTN: hypertension.

newly developed targeted therapies for metastatic renal cell carcinoma [2,3]. The reported incidence of all-grade HTN ranges from 25% with sorafenib and sunitinib, to 40% with axitinib and pazopanib. In addition, multiple case reports have described acute hypertensive complications of therapy with anti-VEGF therapies such as malignant HTN and posterior reversible encephalopathy syndrome [4,5].

Physiologically, HTN develops when inhibition of VEGF causes a decrease in production of nitric oxide and prostacyclin in vascular endothelial cells (Fig. 1) [6]. There is evidence to suggest that HTN may result from structural or functional vascular rarefaction caused by inhibition of angiogenic growth factors [7].

Side adverse events (SAEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. HTN was defined by either maximum or mean systolic blood pressure (SBP) of at least 140 mmHg or diastolic blood pressure (DBP) of at least 90 mmHg, as measured in the clinic on days 1 and 28 of each 6-week treatment cycle at any time during the study after the first dose of sunitinib.

2. Sunitinib mechanism of action

Sunitinib malate (Sutent; Pfizer, New York, USA) is a multitargeted tyrosine kinase inhibitor used in the treatment of metastatic renal cell carcinomas (RCC) and gastrointestinal stromal tumours, and is under evaluation for other malignancies [8]. Sunitinib malate inhibits the VEGFR type 1 and type 2 (FLT1 and FLT1/ KDR), platelet-derived growth factor receptors, stem cell factor receptor (c-KIT) and FLT3 and RET kinases

In a randomized phase III trial in first-line therapy for metastastic renal cell carcinoma [9,10], sunitinib was superior to interferon-α in progression-free-survival (PFS; 11 vs 5 months; $p < 0.001$) and objective response rate (ORR; 47% vs 12%; $p < 0.001$); in addition, median overall survival (OS) with sunitinib was 26.4 vs 21.9 months with interferon-α. Based on these data, sunitinib is currently one of the choices in the treatment for patients with advanced renal cell carcinoma.

Toxicity of sunitib was acceptable; all-grade and grade 3–4 HTN occurred in 30% and 12% of patients treated with this drug, respectively [10]. In the sunitinib expanded-access study, the incidence of all-grade HTN was 22% and grades 3–4 was 5% [11]. Inhibition of the VEGF receptor might increase vascular resistance, caused by decreased nitric oxide and prostacyclin production, as well as provoke vascular rarefaction and increased arterial stiffness, resulting in HTN [12].

Sunitinib treatment-induced HTN was associated with statistically significantly improved clinical outcome. These findings support the hypothesis that HTN may be a viable biomarker of antitumor efficacy in this patient population, although development of HTN during sunitinib treatment was neither necessary nor sufficient for clinical benefit in all patients.

3. Sunitinib induced hypertension

Although several reports have been published on the pathogenesis of HTN secondary to VEGF signaling inhibitors, it exact molecular mechanisms behind has not yet been clearly elucidated. Nitric oxide pathway inhibition decrease in the density of microvessels (rarefaction), increase in oxidative stress, imbalance between endothelin-1 (ET-1) and VEGF, glomerular injury developing from loss of VEGF effect, and changes in neurohormonal factors or the renin-angiotensin-aldosterone represent some of the main proposed mechanisms [13,14].

Previous studies have shown that VEGFR-2 is involved in the regulation of vascular tone. Activation of VEGFR-2 via phosphoinositide 3-kinase (PI3K) and its downstream serine protein kinase (Akt) stimulates endothelium-derived nitric oxide syntase, leading to the production of the potent vasodilator NO. In addition, decreased NO bioavailability disturbs the balance between the vasodilator NO and ET-1, favoring ET-1 production and thereby inducing further vasoconstriction and an additional rise in blood pressure [15,16]. Indeed, plasma ET-1 concentrations have been shown to increase in sunitinib treated patients [17].

Predisposing factors for the development of HTN during treatment with TKIs included gene polymorphims associated with the regulation of blood pressure. In a study in patients with metastatic renal cell carcinoma and GIST, several single-nucleotide polymorphisms (SNPs) in specific genes encoding for metabolizing enzymes, efflux transporters, and drug targets were associated with sunitinib-induced toxicities [18]. Polymorphisms in VEGFA, VEGFR-2 and in the downstream mediators eNOS and ET-1 may be important factors in blood pressure changes [7]. The analysis on polymorphisms genes showed that, during sunitinib therapy, an ACG haplotype in VEGFA is significantly associated with greater elevations in the levels of systolic blood pressure and also with the incidence of grade 3 HTN. In addition, the presence of and eNOS -786 allele was related to a increase in the risk of grade 3 HTN [19].

3.1. Oxidative stress

The shear stress-induced activation of eNOS seems to be dependent on the activation of the PI3K/Akt pathway [20]. Akt has been reported to be activated by Ca^{++}-dependent stimulation of calmodulin-dependent protein kinase. However, the shear-stress-induced phosphorylation of Akt was completely unaffected by the removal of extracellular Ca^{++}. Taken together, research published results show that the stimulation of PI3K/Akt by shear stress and VEGF elicits the serine phosphorylation of eNOS, and thereby enhances enzyme activity in a Ca^{++}-independent manner [20].

VEGF-dependent and VEGF-independent (shear stress) activation of VEGFR-2 gives rise to the increased production of NO and prostacyclin in vascular endothelial cells [21]. Inhibition of these vasodilatory mechanisms subsequently results in increased peripheral vascular resistance and HTN. Increased endothelial shear stress can activate eNOS activity directly, presumably through a VEGF-independent mechanism [20]. Although shear-stress-mediated phosphorylation of eNOS is thought to regulate enzyme activity, the mechanism of activation of eNOS is not yet known.

3.2. Rarefaction

Another possible mechanism causing HTN relates to a decrease in the number of small arteries and arterioles (rarefaction) in response to VEGF kinase inhibitors. New clinical data support the appearance of rarefaction in patients treated with VEGF inhibitors [7]. Studies in hypertensive rat models shows that rarefaction is an early event during HTN. Noon et al. suggested that capillary rarefaction in young adults with a familial predisposition to HTN (as a result of defective angiogenesis) was a cause rather than a consequence of HTN [22]. Microvascular rarefaction has been consistently demonstrated in adults with HTN.

Despite the fact that is unclear whether the rarefaction is structural (disappearance of capillaries), functional (non-perfusion of capillaries), or a contribution of both, it is likely that this phenomenon contributes to the HTN observed in patients treated with VEGF kinase inhibitors.

3.3. Imbalance between ET-1 and VEGF

Endothelial dysfunction reduces nitric oxide production and leads to vasoconstriction. Enhanced secretion of ET-1, a potent vasoconstrictor peptide from endothelial cells [7] result in increased peripheral resistance. However, ET-1 is more likely to influence the local vascular bed than systemic vascular bed.

Some authors have demonstrated a stimulatory interaction between VEGF and ET-1 on each other's gene expression in arterial endothelial cells and vascular smooth muscle cells, suggesting an interplay between these two important pathways that regulate vascular tone [23]. Therefore, it is possible that VEGF kinase inhibitors drugs could cause an imbalance between ET-1 and VEGF, thus contributing to HTN.

3.4. Glomerular injury

VEGF inhibition may also contribute to HTN by other mechanisms: the proximal tubule natriuretic response to elevated blood pressure is partially dependent on cGMP, and VEGF-targeted therapies might suppress this response, perpetuating the rise of blood pressure. In patients on VEGF inhibitors, albumin/creatinine ratio was elevated, and there was a higher incidence of macroalbuminuria than in patients not on VEGF inhibitors [24].

Inhibition of podocyte-endothelial cell VEGF signaling causes endotheliosis, thrombotic microangiopathy, and narrowing of the capillary lumen, the pathological lesion seen in human kidney biopsy specimens from patients with albuminuria receiving VEGF-targeted therapies [24].

3.5. The nitric oxide signaling pathway

NO was originally recognized as a free radical signaling molecule that was naturally produced in the human body. The endogenous source of NO in the body was early discovered to be secondary to metabolism of L-arginine by a family of enzymes known as NO synthases (NOSs). These enzymes utilize the substrates L-arginine, molecular oxygen, and NADPH to produce L-citrulline and NO (Fig. 1). Two of the NOS isoforms are expressed constitutively (endothelial NOS, NOS-III, or eNOS and neuronal NOS, NOS-I, or nNOS), whereas one isoform is inducible in multiple cell types and tissues (inducible NOS, NOS-II, or iNOS) eNOS, as it own name implies, is produced by the vascular endothelium and is the most important isoform in regulating NO production to influence the vascular system.

NO is a highly reactive, diffusible molecule, with a short half-life. This makes it an ideal signaling molecule to act in an autocrine or paracrine fashion. NO regulates vasodilation via effects on soluble guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) [25–27]. Other important vasoregulatory properties of NO include regulation of smooth muscle cell proliferation and migration, platelet aggregation, and leucocyte adhesion to the endothelium.

Also it has been discovered that NO could be produced endogenously in the body via an L-arginine and NOS-independent mechanism from the anion nitrite ($NO2-$) [28]. Nitrite was thought to be a relatively stable end-product of NO metabolism that had no significant biological action. Bryan et al. showed that affects cyclic GMP production, cytochrome P450 activities, and heat shock protein 70 and heme oxygenase-1 expression in a variety of tissues [29].

The arginine/NOS/NO pathway appears be very important in regulating vascular tone and remodeling in blood pressure(BP). Changes in NOS expression and increased NO generation are generally interpreted to be a protective compensatory response to the underlying disease processes that increase vascular resistance. The vasodilatory properties of NO are well characterized and are clearly important in the setting of BP. NO can decrease smooth muscle cell proliferation, but may also protect via increased apoptosis or autophagic signaling to limit the progression of vascular lesions and to remodel the vascular wall [30].

Nitric oxide produced by the endothelial NO synthase is a fundamental determinant of cardiovascular homeostasis: it regulates systemic BP, vascular remodeling and angiogenesis [26]. Physiologically, the most important stimulus for the continuous formation of NO is the viscous drag (shear stress) generated by the streaming blood on the endothelial layer.

3.6. Vascular endothelial growth factor

Vascular endothelial growth factor plays a fundamental role in physiological and pathologic angiogenesis. As a potent mitogen specifically for endothelial cells, VEGF has been shown to promote endothelial cell proliferation and migration in vitro and to induce a strong angiogenic response in peripheral vascular ischemia [13,31].

Although the characteristics of VEGF in pathologic angiogenesis have been extensively studied, the mechanism responsible for VEGF-induced vasodilation is not completely clear. VEGF initiates vasodilation or vasorelaxation in vitro and in vivo [13]. In animals, VEGF induces endothelium-dependent vasorelaxation or vasodilation, in which nitric oxide, but not PGI2, is found to be the main regulator. VEGF exerts multiple biologic effects through its interaction with two receptor tyrosine kinases, Flt-1 (VEGF receptor 1) and KDR (VEGF receptor 2). Flt-1 is required for endothelial morphogenesis, and KDR is involved primarily in mitogenesis [32].

VEGF stimulates production of vasodilatory nitric oxide via activation of endothelial NO synthase and also upregulates vasodilatory prostacyclin. Small molecule VEGF-targeted therapies inhibit the nitrate pathway in vitro, and in humans, HTN often develops within the first few days of treatment, consistent with acute suppression of NO-and/or prostacyclin-mediated vasodilation [33].

Vascular endothelial growth factor exerts vasodilation-induced hypotension, which is likely mediated by oxide nitric and prostaglandin I2. The hypotension induced by acute administration of VEGF is transient and dose-rate dependent and usually can be tolerated in normal animals. VEGFR-2 is the predominant receptor that mediates production of nitric oxide and prostacyclin by endothelial cells, leading to vasodilation. In contrast, inhibition of VEGFR signaling increases blood pressure [2].

Studies have shown that separate genetic polymorphisms in the genes encoding VEGF-A and its main receptor, VEGFR-2, predispose to either tumor response or the development of HTN in patients treated with sunitinib.

Table 1
Antihypertensive drugs.

Class	Drug	Dose
ACE inhibitors	Enalapril	5–40 mg/12–24 h
	Lisinopril	5–20 mg/12–24 h
ARA II	Valsartan	80–320 mg/24 h
	Irbesartan	150–300 mg/24 h
Thiazides	Hydrochlorothiazide	12.5–50 mg/24 h
	Chlorthalidone	12.5–25 mg/24 h
Beta-blockers	Bisoprolol	2.5–10 mg/24 h
	Nebivolol	2.5–5 mg/24 h
Calcium antagonist	Amlodipine	2.5–10 mg/24 h

ACE inhibitors: Angiotensin converting enzyme inhibitors; ARA II: angiotensin II receptor antagonist.

4. Hypertension management

Importantly, the development of hypertension on VEGF-targeted therapy correlates with improved cancer outcomes and, therefore, could represent a biomarker useful for selecting the subset of patients with the best chance of responding to anti-angiogenic therapy.

Before the initiation of sunitinib, patients should be assessed for preHTN. Those showing preHTN should receive antihypertensive treatment for 3–7 days before starting sunitinib, and subsequent regular monitoring of BP is necessary. The selection of antihypertensive medication should be based on the general cardiovascular status of the patient, as well as taking into account interactions and contraindications with other drugs. Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for sunitinib should be considered when it must be co-administered with strong CYP3A4 inhibitors. AS CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations, a dose increase for sunitinib should be considered when it must be co-administered with CYP3A4 inducers [34].

No clear recommendations for specific antihypertensive therapies can be made. Nevertheless, there is some evidence supporting the selection of particular antihypertensive drugs based on the patient's status, as described in the European Society of Cardiology guidelines [35].

Antihypertensive medications included beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineral-corticoid antagonists, and diuretics; the loop diuretic furosemide is excluded as it is frequently prescribed for management of edema (Table 1). Preference for vasodilatory drugs, such as ACEI, angiotensin II receptor blockers, or calcium channel antagonists is based on the vasoconstrictive activity of the tyrosine kinase inhibitors [36]. Additionally, the potential impact of CYP3A4 induction or inhibition with sunitinib should be considered. In this sense, calcium channel blockers, such as verapamil or diltiazem, should be avoided. Although high BP has been proposed to reflect the clinical efficacy of VEGF signal inhibition with targeted treatment, control of HTN is essential to avoid serious adverse events without detrimental antitumor activity.

In most patients, HTN can be controlled with standard antihypertensive drugs. However, the biological effect of these antihypertensive medications on angiogenesis and its implications should be considered. Both enalapril and candesartan can inhibit myocardial angiogenesis induced by VEGF. However, nifedipine has been shown to induce VEGF secretion. Diuretics also have been used successfully to manage increases in BP arising from cancer treatment; however, thiazide-type diuretics should be used cautiously, particularly in patients prone to dehydration or hypercalcemia [37].

The vasodilatory effect of NO has led to explore its use as a hypotensive agent in patients treated with tyrosine kinase inhibitors. Nitrovasodilators such as glyceryl trinitrate, isosorbide mononitrate and sodium nitroprusside act by releasing NO into the vascular smooth muscle. They donate NO through mechanisms involving the thiol groups of intracellular proteins [38].

Sodium nitroprusside produces hypotension by increasing the NO-mediated generation of cGMP, which in turn causes vasodilation. In addition, phosphodiesterase type 5 inhibitor augments nitroprusside-induced hypotension.

Kruzliak et al. reported the use of NO donors in 3 patients treated with bevacizumab +/- chemotherapy. All patients developed HTN resistant to combinations of three or more clasic antihypertensive drugs. However the BP normalized after use of molsidomide, isosorbide dinitrate and isosorbide mononitrate, respectively [39]. The autors conclude that NO donors could be successfully used not only for the treatment of developed angiogenesis-inhibitor-induced HTN but also for preventive effects.

In a later study Kruzliak et al. proposes a treatment algorithm, distinguishing 3 groups of patients [40]:

1. Normotensive patients($<120/<80$ mmHg). Blood pressure measurement every two weeks, subsequently spaced if HTN is not developed. No pharmacological trtamiento is needed.
2. Prehypertensive patients (120–130/80–89 mmHg). Weekly initial BP measurement. It is not necessary to start drug treatment unless organ damage is detected; in this case start NO donors
3. Hypertensive ($>140/>90$ mmHg). Weekly initial BP measurement. Start with NO and if blood pressure is not controlled add other drugs.
4. In conclusion,VEGF signaling pathway has been recognized as an important player in the development of RCC. Angiogenesis inhibitors are useful drugs in the treatment of this disease, but are associate with several side effects, with HTN being the most common one. VEGF inhibitors-induced decrease in nitric oxide synthase and nitric oxide production, that can result in vasoconstriction and increased blood pressure. So NO donors may be drugs of choice in the treatment of HTN associated with TKI, and is necessary to explore prospectively its use to confirm these promising initial results.

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