Published in final edited form as:

Trends Cardiovasc Med. 2013 May ; 23(4): 104–113. doi:10.1016/j.tcm.2012.09.008.

Cardiovascular Complications Associated with Novel Angiogenesis Inhibitors: Emerging Evidence and Evolving Perspectives

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Abstract

Novel cancer therapies targeting tumor angiogenesis have revolutionized treatment options in a variety of tumors. Specifically, VEGF signaling pathway (VSP) inhibitors have been introduced into clinical practice at a rapid pace over the last decade. It is becoming increasingly clear that VSP inhibitors can cause cardiovascular toxicities including hypertension, thrombosis, and heart failure. This review highlights these toxicities and proposes several strategies in their prevention and treatment. However, we recognize the dearth of data in this area and advocate a multi-disciplinary approach involving cardiologists and oncologists, as well as clinical and translational studies, in understanding and treating VSP-inhibitor associated toxicities.

Introduction

Angiogenesis and Cancer Therapy: A Historical Perspective

Over forty years ago, Judah Folkman observed an association between solid tumor growth and vascular supply. Folkman and colleagues showed that a soluble factor isolated from tumor tissue, which they termed "tumor angiogenesis factor (TAF)", could promote neovascularization of tumors *in vivo* (Folkman et al., 1971). They suggested that inhibition of TAF at an early stage in tumor growth could prove an effective therapeutic strategy in cancer patients (Sherwood et al., 1971). In 1983, Dvorak and Senger identified a factor produced by tumor cells, called vascular permeability factor or VPF, that promoted vascular hyperpermeability and ascites accumulation (Senger et al., 1983). In 1989, Ferrara and colleagues isolated and sequenced vascular endothelial growth factor (VEGF), which they

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determined to be synonymous with VPF (Keck et al., 1989; Leung et al., 1989). In the decades following these early observations, our understanding of angiogenesis in tumor biology has broadened substantially, as has our ability to pharmacologically target angiogenic pathways. Inhibiting angiogenesis by targeting specific pro-angiogenic factors has become a major focus of cancer drug development. In particular, VEGF signaling pathway (VSP) inhibition has led to the development of a number of drugs that are now in use to treat a variety of malignancies (Figure 1).

VEGF (formally called VEGF-A) is one of five members of a family of structurally related proteins that are involved in the regulation of vascular and lymphatic endothelium. Members of this family bind to receptor tyrosine kinases (RTKs) referred to as VEGFR1, VEGFR2, and VEGFR3, all of which are characterized by specific tissue distributions and functions. The pro-angiogenic effect of VEGF is mediated primarily through VEGFR2 on endothelial cells. Upon ligation and autophosphorylation of VEGFR2, numerous intracellular signaling pathways are activated and mediate the effects of VEGF on endothelial cell survival, proliferation, and migration (Figure 2).

The VEGF pathway can be targeted at numerous steps in the signaling cascade, and indeed, existing VSP inhibitors work by either blocking VEGF-VEGR2 ligation or by inhibiting downstream intracellular signaling components (Figure 1). Currently, there are six VSP inhibitors approved for the treatment of various malignancies and numerous compounds in various stages of preclinical or clinical development (Table 1).

Bevacizumab is a fully humanized monoclonal antibody that binds and neutralizes VEGF. In 2004, it became the first VSP inhibitor approved by the U.S. Food and Drug Administration after a seminal study showed that bevacizumab plus conventional chemotherapy conferred increased overall survival in patients with metastatic colorectal cancer compared with conventional chemotherapy alone (Hurwitz et al., 2004). It has since been approved as either combination therapy or monotherapy in unresectable, advanced non-squamous non-small cell lung cancer, metastatic breast cancer, metastatic renal cell carcinoma, and recurrent glioblastoma. Of note, in November 2011 the FDA revoked approval for bevacizumab for the treatment of metastatic breast cancer after the FDA determined minimal anti-tumor efficacy (Dienstmann et al., 2012).

The approval of bevacizumab has been followed by FDA approval of five additional VSP inhibitors for various cancer types. Sunitinib (Sutent), sorafenib (Nexavar), pazopanib (Votrient), axitinib (Inlyta), and vandetanib (Caprelsa) are all small molecule multiple tyrosine kinase inhibitors (TKIs) with varying specificities for VEGF receptors. Because the kinase domains in the VEGFRs share structural similarity with the kinase domains in other signaling receptors, these TKIs target multiple pathways. Sunitinib shows activity against all three VEGFRs, PDGFR α and β , KIT, FLT3. It has been approved for the treatment of gastrointestinal stromal tumor following progression or the development of resistance to imatinib, advanced renal cell carcinoma, and advanced pancreatic neuroendocrine tumors. Sorafenib targets VEGFRs, platelet-derived growth factor receptor- β (PDGF- β), stem cell factor receptor (KIT), Fms-like kinase receptor 3 (FLT3), and RET, as well as the intracellular kinases CRAF, BRAF, and mutant BRAF and has been approved for the treatment of advanced hepatocellular carcinoma and advanced renal cell carcinoma. Pazopanib has activity against VEGFRs, PDGFRs, fibroblast growth factor receptors (FGFRs) -1 and -3, and has been approved for the treatment of mRCC and advanced soft tissue sarcoma that have received prior chemotherapy. Most recently, vandetanib and axitinib were approved for the treatment of locally advanced or metastatic medullary thyroid cancer and renal cell carcinoma, respectively. It is important to note the relative promiscuity of these TKIs, especially as this may have significance with respect to toxicities associated

with these compounds. Nevertheless, for the rest of this review, we will refer to these therapies as VSP inhibitors, since VEGF receptors are a common target.

Despite the recent explosion of novel VSP inhibitors granted FDA approved or in various stages of clinical trials, the benefit of these agents has been modest. More importantly, VSP inhibitors are associated with a number of clinically important adverse events. At least two recent meta-analyses suggest an increased risk of fatal adverse events in patients treated with VSP inhibitors compared to placebo (Ranpura et al., 2011; Schutz et al., 2012). This manuscript will review the incidence, potential mechanisms of action and treatment strategies for cardiovascular toxicities associated with VSP inhibitors. These include risks for hypertension, thromboembolic disease, and heart failure (Table 2). We will review the emerging data implicating cardiovascular toxicities associated with these agents, discuss potential mechanisms for these toxicities, and treatment strategies that we utilize in the clinical setting to treat these complications.

VSP Inhibitors and Adverse Cardiovascular Events

Hypertension

Incidence—Hypertension is the most common cardiovascular toxicity associated with VSP inhibitors and has been observed in every trial involving these agents. A number of recent reviews have focused on the topic (Maitland et al., 2010; Robinson et al., 2010a; Nazer et al., 2011).

Several meta-analyses have shown an incidence of hypertension of 19–25% with FDA approved VSP inhibitors. While the incidence is probably lower in patients treated with bevacizumab, a higher incidence of hypertension is observed with newer VSP inhibitors such as axitinib and cediranib (Wu et al., 2008). A recent study of women treated with cediranib, for example, found that 87% of patients had hypertension by the end of the study (Robinson et al., 2010a). Almost 100% of patients treated with VSP inhibitors have an absolute increase in blood pressure although only a subset develop hypertension (Maitland et al., 2009). Blood pressure increase is rapid in most patients and for this reason, NCI protocols recommend weekly blood pressure monitoring after the first cycle of therapy and at least every 2–3 weeks thereafter (Maitland et al., 2010). Interestingly, blood pressure changes seen after the initiation of VSP inhibitor therapy can be reversible once chemotherapy is stopped, an observation that has implications for patient management (Azizi et al., 2008).

The meta-analyses of cancer clinical trials where the incidence of hypertension has been studied probably underestimate the true incidence of hypertension in “real-life” cancer patients. Patients with difficult-to-treat hypertension are generally excluded from enrollment in clinical trials whereas these restrictions do not apply to the use of chemotherapies once FDA approved. In addition, initial trials with VSP inhibitors used less strict criteria for defining hypertension than those defined by JNC7 guidelines (Nazer et al., 2011). On the other hand, much of the risk associated with hypertension in the JNC7 guidelines implicate *long-term* morbidity and mortality of increased blood pressure. In cancer patients receiving treatment with VSP inhibitors, where life expectancy could be limited by cancer, the goal may not be preventing long-term effects of hypertension, but rather, limiting short-term complications of hypertension such as congestive heart failure or stroke.

Mechanism—There are several proposed mechanisms for VSP inhibitor-associated hypertension (see Table 3). Both functional and anatomic changes in the endothelium appear to promote increased vascular resistance leading to hypertension. VEGF biology suggests a central role for nitric oxide (NO), although a number of studies suggest a more complex

picture. Activation of VEGFR2, either through VEGF ligation or by flow-mediated shear stress (Jin et al., 2003) activates phosphatidylinositol 3 kinase (PI3K) and AKT kinase, leading to downstream activation of endothelial nitric oxide synthase (eNOS) as well as increased production of other potent vasodilators such as PGI₂ (He et al., 1999; see figure 2). Consistent with this model, VEGF induces NO production (van der Zee et al., 1997) and results in a NOS-dependent decrease in blood pressure (Horowitz et al., 1997; Fulton et al., 1999; Facemire et al., 2009). While some studies in rodents, as well as in patients treated with VSP inhibitors, show decreased urinary nitrite/nitrate excretion and reduced levels of serum NO metabolites (Kappers et al., 2010; Robinson et al., 2010b; Mayer et al., 2011), other studies demonstrate a less certain role for NO in VSP-inhibitor associated hypertension (Kappers et al., 2012). In addition, a recent small prospective study of breast cancer patients treated with vandetanib showed no difference in flow-mediated dilation, a surrogate for NO bioavailability despite decreased serum nitrate/nitrite levels compared to baseline (Mayer et al., 2011). Further complicating this picture is emerging evidence implicating endothelin-1 (ET-1), a potent vasoconstrictor, in VSP inhibitor mediated hypertension (Kappers et al., 2011). Whether the effect of VSP inhibitors on systemic blood pressure is due primarily to modulation of NO, ET-1, or both will require further investigation.

VEGF signaling plays an important role for maintaining endothelial cell viability and structure. VEGF promotes endothelial cell survival and, conversely, inhibition of VEGF leads to endothelial cell apoptosis and chronic remodeling of the capillary beds, a process referred to as capillary rarefaction (Gerber et al., 1998; Baffert et al., 2006). Human studies demonstrate a significant decrease in dermal capillary density and decreased capillary dilatory response after VSP inhibitor treatment, implicating functional as well as anatomic attenuation of vessel density (Mourad et al., 2008; Steeghs et al., 2008). Interestingly, decreased capillary density was reversible after cessation of bevacizumab treatment (Steeghs et al., 2010), consistent with observed clinical reversal of hypertension after cessation of VSP inhibitor treatment. Capillary rarefaction in the heart may also be a contributor to VSP inhibitor associated cardiomyopathy (see below).

Interesting similarities exist between VSP inhibitor-associated hypertension and pre-eclampsia, a syndrome of hypertension and proteinuria affecting 5% of all pregnancies. As in pre-eclampsia, proteinuria is often noted with VSP-inhibitor associated hypertension. These observations have implications for our understanding of the pathogenesis as well as the management of VSP inhibitor-related hypertension (see below). Importantly, pre-eclampsia has been associated with decreased VEGFR signaling as a result of elevated levels of soluble VEGFR (Maynard et al., 2003). Moreover, systemic endothelial dysfunction, a central feature in patients with pre-eclampsia, may play a pathological role in VSP inhibitor-associated vascular thromboses (see below).

Management—Observations from early clinical trials involving VSP inhibitors, the elucidation of potential mechanisms of toxicity, and the emerging focused multi-disciplinary clinics (such our cardio-oncology clinic at Dana-Farber Cancer Institute, www.cardio-onc.org) have helped develop early management strategies for VSP inhibitor associated hypertension. However, these early recommendations must be solidified by additional clinical studies.

In all patients considered for VSP inhibitor treatment, blood pressure needs to be aggressively managed prior to initiation of chemotherapy and in keeping with JNC7 guidelines. Blood pressure monitoring should be performed frequently, at least weekly, for the first six weeks of treatment. High-risk patients should be urged to use an automated home blood pressure cuff to monitor blood pressure at home. Because VSP inhibitors have

been associated with proteinuria, testing for urine proteins should be performed before and after initiation of treatment and select patients should be referred to a nephrologist. We suggest spot urine for protein and creatinine to allow for the calculation of the urine protein/creatinine ratio (UPC) ratio. A simple urinalysis may not be an optimal test to quantify the amount of protein in the urine because results are susceptible to fluctuations in the water content of the urine. The gold standard for protein quantification remains a 24-hour urine collection, but the UPC ratio usually correlates well with the 24-hour urine test and is less cumbersome.

While lifestyle modification (moderating alcohol intake and reduced dietary salt) should be encouraged with all patients, many patients will need pharmacological treatment of hypertension. We advocate angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers as a first- and second-line therapy (Nazer et al., 2011). In particular, nondihydropyridine calcium channel blockers (verapamil and diltiazem) should be avoided in patients with TKIs such as sunitinib and sorafenib because of the formers' inhibition of the CYP3A4 system, by which the TKIs are metabolized. Hypertension can be difficult to manage in some patients at which point additional anti-hypertensive medications or VSP inhibitor dose reduction or interruption may need to be considered. Finally, because of the reversibility of VSP-inhibitor hypertension, blood pressure medications may need to be titrated during chemotherapy "holiday," such as in the 4 weeks-on/2 weeks-off schedule of sunitinib.

Arterial and Venous Thromboembolism

Incidence—It is well established that malignancy is associated with a hypercoagulable state. Numerous studies have suggested that the incidence of thromboembolic events in patients treated with VSP inhibitors is further increased compared to control groups. Both arterial and venous thromboembolic events (ATE and VTE, respectively) in the setting of VSP inhibitor therapy have been examined in meta-analyses (Nalluri et al., 2008). Nalluri et al. conducted an analysis of 7,956 patients and found that the incidence of all-grade VTEs ranged from 3% to 19.1%, depending on tumor type; the summary incidence was 11.9%. The incidence of high-grade VTEs in patients on bevacizumab in combination with other chemotherapeutic agents ranged from 2 to 17%, with an overall incidence of 6.3%. The relative risk of all-grade VTE in patients on bevacizumab versus control was found to be 1.33. A subsequent study by Hurwitz and colleagues sought to address limitations in the previous study and found that, in contrast, there was no significant difference in the incidence rates of VTE in patients receiving bevacizumab compared to controls (Hurwitz et al., 2011). Additional prospective studies are needed to further clarify the risk of VTE in the setting of VSP inhibition.

The occurrence of arterial thromboembolic events has been more consistent across studies. One group conducted a pooled analysis of 1,745 patients from five RCTs and found an increased risk of ATE in patients receiving bevacizumab vs. control (3.8% vs. 1.7%; (Scappaticci et al., 2007). A 2010 meta-analysis included 20 RCTs and found a relative risk of ATE of 1.44 in patients receiving bevacizumab compared to controls. Relative risk of high-grade myocardial ischemia in patients taking bevacizumab was also increased relative to controls (Ranpura et al., 2010). Additional meta-analyses have shown consistent incidence rates of ATEs with respect to bevacizumab therapy (Schutz et al., 2011; Tebbutt et al., 2011).

Choueiri and colleagues conducted a meta-analysis to examine the risk of ATE in patients taking sunitinib and sorafenib. They found that among 9,387 patients, the use of either sunitinib or sorafenib was associated with a 1.4% incidence of all-grade ATE with a relative risk of 3.03 in patients receiving either sunitinib or sorafenib compared to placebo. While

these results are intriguing, they need be replicated in prospective studies to more fully clarify the risk of thromboembolism in patients taking these small molecule inhibitors.

Interestingly, although VSP inhibitors have been associated with increased risk of thromboembolic events, they are also paradoxically associated with a risk of bleeding and hemorrhage. A number of meta-analyses have examined the risk of these adverse events in patients taking bevacizumab and consistently shown a dose-dependent increase in the relative risk of bleeding, as well as a significantly increased risk of high-grade bleeding events (Geiger-Gritsch et al., 2010; Hapani et al., 2010; Hang et al., 2011). Je and colleagues conducted a meta-analysis of bleeding risk in patients on sunitinib and sorafenib and found an increased incidence and relative risk of all-grade bleeding events (16.7% and 2.0, respectively) relative to control patients (Je et al., 2009). Another recent meta-analysis assessed the risk of fatal adverse events (FAEs) associated with the use of the sunitinib, sorafenib, and pazopanib and found that the RR of experiencing a FAE was 2.23 compared to control patients and that hemorrhage was the FAE occurring most commonly (47.5%). In this study, myocardial infarction was the second most common, accounting for 15% of FAEs (Schutz et al., 2012).

Mechanisms—It is clear from clinical studies that the hemostatic balance is significantly altered in patients on VSP inhibitors. A number of mechanisms have been proposed. The endothelium plays a crucial role in maintaining hemostasis and alterations in endothelial cell function can shift the hemostatic balance in favor of either thrombosis or hemorrhage. VEGF plays an important role in modulating these processes by affecting endothelial cell function, proliferation, and survival. For example, studies have demonstrated the effect of VEGF on endothelial cell survival (Alon et al., 1995; Gerber et al., 1998). Gerber and colleagues demonstrated that VEGF promotes survival of HUVEC cells by activating the PI3K-AKT pathway. Other groups have demonstrated that stimulation of VEGF results in the upregulation of both anti-apoptotic (e.g. bcl-2, survivin) and pro-survival (e.g. eNOS) signals (Dimmeler et al., 1999; Fulton et al., 1999; Tran et al., 1999). The dominant hypothesis is that inhibition of VEGF signaling results in decreased endothelial cell survival and increased apoptosis in response to vascular injury leading to disruption of the endothelial cell barrier and exposure of subendothelial von Willebrand factor (vWF) and tissue factor (TF) followed by platelet aggregation and the formation of thrombus.

In addition to maintaining a functional endothelial barrier, there is evidence that VEGF may also modulate the expression of numerous factors involved in both hemostasis and thrombolysis. NO and PGI₂ are both inhibitors of platelet activation that are well known to be increased upon EC stimulation with VEGF (Tsurumi et al., 1997; van der Zee et al., 1997; Wheeler-Jones et al., 1997). Furthermore, the thrombolytic serine proteases urokinase-protease activator (u-PA) and tissue type plasminogen activator (t-PA) have been shown to be upregulated by VEGF (Pepper et al., 1991). Paradoxically however, VEGF stimulation of ECs can also induce expression of TF, but increased surface expression is only observed upon co-stimulation with TNF α (Camera et al., 1999). Clearly the role of VEGF in modulating hemostasis and thrombosis is complex and the extent to which these mechanisms contribute to VSPI-associated thromboembolism and hemorrhage are not entirely clear.

An alternative and intriguing hypothesis put forth by Meyer *et al.* is that thrombosis associated with the use of bevacizumab results from immune complex (IC)-mediated activation of platelets (Meyer et al., 2009). Bevacizumab forms ICs with VEGF, the latter of which can interact with heparin (Gitay-Goren et al., 1992; Ito and Claesson-Welsh, 1999). The formation of bevacizumab-VEGF-heparin complexes can bind and subsequently activate platelets through the Fc γ RIIa receptor, similar to what is thought to occur in

heparin-induced thrombocytopenia (HIT). One interesting question that emerges from this hypothesis is whether genetic variations might confer an increased risk for development of thromboembolism in the setting of bevacizumab therapy and if so, whether patients at greatest risk might be identified prior to bevacizumab treatment.

Management—It is clear that prospective studies are needed to further clarify the risk that VSP inhibitors in patients with respect to thromboembolic events. In our clinic, patients with a previous history of coronary artery disease or other ischemic events are placed on VSP inhibitors with caution. Management of such patients should include aggressive secondary prevention of blood pressure control. Although no consensus exists with respect to the use of prophylactic anti-platelet therapy, in our clinic we initiate either aspirin or clopidogrel in select high-risk patients before treatment. These include patients with previous coronary or peripheral vascular disease.

Left Ventricular Dysfunction and Cardiomyopathy

Incidence—Emerging clinical studies suggest that treatment with VSP inhibitors can have a detrimental effect on cardiac function. A meta-analysis assessing five clinical trials (and involving 3,784 patients with breast cancer) showed an incidence of high-grade congestive heart failure (CHF) to be 1.6% in patients treated with bevacizumab compared to 0.4% in the control or placebo groups, resulting in an overall RR of developing high-grade CHF of 4.74. In this analysis, concomitant chemotherapy did not significantly affect overall RR (Choueiri et al., 2011). The propensity of patients receiving sunitinib to develop CHF has also been evaluated in another meta-analysis by Choueiri and colleagues. A total of 6,935 patients from 16 studies were included in the analysis. The overall incidence of all-grade and high-grade CHF was 4.1% and 1.5%, respectively. The investigators found that treatment with sunitinib was associated with an increased relative risk of developing all-grade and high-grade CHF (RR of 1.81 and 3.30, respectively).

The above meta-analyses, however, probably underestimate the true incidence of cardiomyopathy in the setting of VSP inhibitor treatment for several reasons (Force and Kerkela, 2008; Witteles and Telli, 2012). First, none of these clinical trials prospectively monitored cardiac function, thus they relying heavily on investigator judgment of clinical heart failure. Second, reporting of heart failure using NCI's Common Terminology Criteria of Adverse Events (CTCAE) can be confusing given the various definitions for cardiomyopathy (Witteles and Telli, 2012). Third, diagnosis of heart failure in cancer patients can be difficult given the often non-specific symptoms that can arise with malignancy (such as fatigue or peripheral edema). Fourth, cardiomyopathy can present as asymptomatic left ventricular dysfunction, thus underscoring the necessity of cardiac imaging in the clinical trials (which are generally not done). Fifth, long term consequences of VSP inhibitors with respect to the heart are completely unknown. Finally, early clinical trials with novel cancer therapies usually exclude patients with a history of significant heart failure, uncontrolled hypertension, or other risk factors whereas these exclusions do not always apply to the general population once a drug is FDA approved.

Retrospective observational data from individual trials involving VSP inhibitors suggest a significant incidence of cardiomyopathy. Among 75 patients with imatinib-resistant gastrointestinal stromal tumor in a phase I/II trial of sunitinib, 28% of patients had an absolute decrease in ejection fraction (Chu et al., 2007). Other studies from single institutions suggest an increased incidence of cardiomyopathy although some of these studies used a loose definition for cardiotoxicity. For example, an observational study of patients with metastatic renal cell carcinoma treated with sunitinib or sorafenib found that 33% patients had a "cardiac event," although "cardiac event" ranged from an asymptomatic

increased cardiac enzymes to a new left ventricular dysfunction requiring intensive care (Schmidinger et al., 2008). In the future, prospective studies using close clinical and imaging follow-up of patients treated with VSP inhibitors are needed to get a better estimation of patients who develop left ventricular dysfunction.

Mechanism—There have been several proposed mechanisms for VSP inhibitor-associated heart failure. The most intriguing model is derived from animal studies of VEGF inhibition in the heart. Keshet and colleagues show reversible cardiomyopathy in a mouse model using a tunable transgene encoding a VEGF trap. The induction of the VEGF trap leads to decreased capillary density (similar to capillary rarefaction), induction of hypoxia and hypoxia-inducible genes in the myocardium, as well as cardiac dysfunction, which is reversible upon removal of the transgene (May et al., 2008). It remains to be seen whether a similar mechanism is at play in humans treated with VSP inhibitors although, consistent with this model, many cases of VSP inhibitor-associated cardiomyopathy are reversible (Chu et al., 2007; Uraizee et al., 2011). Nevertheless, because of the relative promiscuity of sunitinib and sorafenib, other pathways besides VEGF may be involved. Besides VEGF receptor activity, for example, many of VSP inhibitors, also inhibit PDGF signaling. Transverse aortic constriction (TAC) of mice where PDGF receptor β is genetically knocked down in cardiomyocytes, for example, leads to decreased capillary density, increased tissue hypoxia and accentuated heart failure (Chintalgattu et al., 2010). On the other hand, Force and colleagues have implicated 5'-adenosine monophosphate-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis in sunitinib-induced heart failure (Kerkela et al., 2009).

Management—In the absence of prospective studies detailing the extent of cardiomyopathy and the absence of established guidelines, we advocate a low threshold on the part of the physician for assessing for cardiac dysfunction in patients treated with VSP inhibitors. We suggest that all patients undergo a baseline echocardiogram to assess for structural heart disease prior to initiation of treatment. Cardiac risk factors including hypertension should be aggressively treated during therapy and a repeat echocardiogram be done if the patient has symptoms concerning for heart failure. Upon detection of cardiomyopathy, VSP inhibitor treatment should be stopped and patients be started on cardioprotective medications including beta-blockers and ACE inhibitors. A multidisciplinary approach including the treating oncologist and cardiologist will provide highly specialized care that will lead to early detection and prevention of potential cardiovascular events (www.cardio-onc.org)

Concluding Remarks

The past decade has seen a remarkable emergence of novel cancer therapeutics. Specifically, drugs that target the VEGF signaling pathway (VSP inhibitors) have been developed and tested at an extraordinary pace. Over the last few years, VSP inhibitors have been associated with a number of toxicities, including cardiovascular toxicities. This review highlights some of these toxicities and proposes several strategies in their prevention and treatment (for summary of recommendations, see table 4). Most of the current data regarding cardiovascular toxicities of VSP inhibitors come from retrospective meta-analyses from clinical trials. In addition, most of the treatment strategies are emerging from multidisciplinary and team-based clinical care groups in cardiology, oncology and nephrology (such as ours at Brigham and Women's Hospital/Dana-Farber Cancer Institute), but these treatment strategies often evolve from physician personal experience rather than tested clinical trials. Furthermore, there remain many unanswered questions with respect to the incidence, pathophysiology, prevention, and treatment strategies for cardiovascular toxicities associated with VSP inhibitors. For example, would traditional medications such as ACE

inhibitors and beta-blockers be protective in VSP-inhibitor associated cardiomyopathy? Which anti-hypertensive agents are most effective in managing VSP inhibitor-associated hypertension? Interestingly, an understanding of VSP inhibitor-associated toxicities may give insight into both tumor and cardiovascular biology. For example, preliminary studies suggest that the severity of cardiovascular toxicity caused by VSP inhibitors may be positively associated with the clinical efficacy of these agents (Robinson et al., 2010a; Österlund et al., 2011). These considerations are important with respect to the biology of VSP inhibitor therapy but also with respect to patient care given the importance of balancing VSP inhibitor-associated toxicities with the benefits obtained in treating malignancy. Six VSP inhibitors are currently approved in the US and it is likely that this number will double in the next five years. As these drugs become more widely available for different indications, addressing these and other questions will be imperative to providing the safest and most effective care.

Acknowledgments

We thank Dr. James Michael Kirshenbaum for critical review of the manuscript. SMB is supported by the Stanley Sarnoff Fellowship. JM is supported by an NIH Career Development Award (K08), Watkins Discovery Award Program and Cardiovascular Leadership Council Investigator Award (both by Brigham and Women's Hospital).

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Figure 1. Mechanisms of VEGF signaling pathway inhibitors

Multiple strategies have been employed to pharmacologically target the VEGF signaling pathway. One anti-VEGF monoclonal antibody has been developed (bevacizumab). Multiple tyrosine kinase inhibitors (TKIs) target the intracellular kinase domain on the VEGF receptors, as well as on other important tyrosine kinases. Five currently approved VSP inhibitors fall into this category (sunitinib, sorafenib, axitinib, pazopanib, and vandetanib). Numerous other TKIs are in various stages of development or trials. Other approaches to VSP inhibition that are currently in development or clinical trials include a soluble VEGF receptor, or VEGF-Trap, and a monoclonal antibody generated against VEGFR2.

Figure 2. Signaling pathways downstream of VEGFR2 in endothelial cells

VEGFR2 is the primary VEGFR that mediates angiogenic signaling. Numerous pathways are activated in response to VEGF binding to VEGFR2. Notably, endothelial nitric oxide synthase (eNOS) is activated by multiple pathways including PKC and AKT/PKB, leading to an increase in vascular permeability and a decrease in vascular resistance. Signaling through Ras and PI3K-AKT promotes cell survival and proliferation. FAK and p38/MAPK signaling promote cellular mobility and migration. These pathways promote increased endothelial cell survival, proliferation, and migration, culminating in increased angiogenic potential. AKT/PKB, protein kinase B; cPLA2, cytoplasmic phospholipase 2; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; MEK, mitogen-activated protein kinase kinase; NO, nitric oxide; PGI₂, prostaglandin I₂; PI3K, phosphatidylinositol-3 kinase; PKC, protein kinase C; PLCγ, phospholipase Cγ; p38/MAPK, mitogen-activated protein kinase.

Table 1**VSP inhibitors in clinical use and development**

Drug Name	Drug Type	Year approved	Current Indications
Bevacizumab	mAb	2004	Metastatic colorectal cancer, advanced NSCLC (in combination with cytotoxic chemotherapy), and renal cell carcinoma (in combination with interferon-alpha immunotherapy); Monotherapy in progressive glioblastoma following previous therapy
Sorafenib	TKI	2005	Hepatocellular carcinoma, renal cell carcinoma
Sunitinib	TKI	2006	Gastrointestinal stromal tumor following progression or resistance to imatinib, advanced renal cell carcinoma, progressive pancreatic neuroendocrine tumors
Pazopanib	TKI	2009	Advanced renal cell carcinoma, advanced soft tissue sarcoma
Vandetanib	TKI	2011	Advanced and metastatic medullary thyroid cancer
Axitinib	TKI	2012	Advanced renal cell carcinoma (second line)

Other VSP Inhibitors in Clinical Development

Ramucirumab – VEGFR2 mAb

Aflibercept – VEGF Trap

Cediranib – TKI

Semaxanib –TKI

Brivanib – TKI

Torceranib – TKI

Regorafenib – TKI

Tivozanib-TKI

Cabozantinib-TKI

* mAb, Monoclonal Antibody; TKI, tyrosine kinase inhibitor

Table 2**Meta-Analyses Conducted to Assess Adverse Events of VSPIs**

Adverse Event	VSP Inhibitor	Citation
Hypertension (HTN)	Bevacizumab	Ranpura et al. 2010
	Sunitinib	Zhu et al. 2009
	Sorafenib	Wu et al. 2008
Venous thromboembolism (VTE)	Bevacizumab	Nalluri et al. 2008
		Hurwitz et al. 2011
Arterial thromboembolism (ATE)	Bevacizumab	Scappaticci et al. 2007
		Ranpura et al. 2010
		Tebbutt et al. 2011
		Schutz et al. 2011
Congestive heart failure (CHF)	Sunitinib, Sorafenib	Choueiri et al. 2010
	Bevacizumab	Choueiri et al. 2011
	Sunitinib	Richards et al. 2011

Table 3

Possible mechanisms for VSP inhibitor-associated hypertension

Mechanism	Evidence
Structural	
Decreased endothelial cell viability	Gerber et al., 1998
Vessel rarefaction	Baffert et al., 2006
	Steeghs et al., 2010
	Mourad et al., 2008
	Steeghs et al., 2008
Functional	
Decreased NO and PGI ₂ production, decreased, vasoconstriction	Horowitz et al., 1997
	Fulton et al., 1999
	Facemire et al., 2009
	Robinson et al., 2010b
Increased ET-1 production, vasoconstriction	Kappers et al., 2011
	Kappers et al., 2012

Table 4

Summary of recommended management strategies for VSP inhibitor cardiovascular complications

Adverse Event	Prior to Treatment		After initiation of treatment	
Hypertension (HTN)	1	Aggressive management of blood pressure consistent with JNC7 guidelines	1	Frequent (weekly) monitoring of blood pressure in the first six weeks
	2	Urine analysis for proteinuria	2	Use of automated home blood pressure cuff for high risk patients
			3	Urine analysis for proteinuria
			4	Aggressive blood pressure management with the use of angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers (1 st and 2 nd line therapy)
			5	Titration of blood pressure medications during chemotherapy “holiday” (if necessary)
Arterial thromboembolism (ATE)	1	Ensure no active angina or symptomatic CAD		
	2	Initiation of anti-platelet therapy in high risk individuals (patients with previous coronary artery disease or peripheral arterial disease)		
Cardiomyopathy	1	Baseline echocardiogram to assess for structural heart disease in all patients	1	Low threshold for repeat echocardiogram if signs or symptoms consistent with cardiomyopathy
	2	Aggressive management of cardiac risk factors (especially hypertension)	2	If cardiomyopathy detected, then prompt stopping of VSP inhibitor and initiation of cardioprotective medications (ACE inhibitors and beta blockers)