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Cardiovascular toxicities: clues to optimal administration of vascular endothelial growth factor signaling pathway inhibitors

Kelly L. Snider and **Michael L. Maitland**
Section of Hematology/Oncology, University of Chicago, 5841 S. Maryland Ave., MC2115, Chicago, IL 60637, USA

Michael L. Maitland: mmaitlan@medicine.bsd.uchicago.edu

Abstract

Several angiogenesis inhibitors have been approved for commercial use and many additional agents are under development for the treatment of various malignancies. Cardiovascular toxicities have been increasingly recognized as effects of this entire class of new anticancer therapeutics. There is a limited but growing understanding of the mechanism of action of these drugs in the human cancer patient and the factors affecting the therapeutic index. In addition to reviewing current concepts for the cardiovascular toxicities of angiogenesis inhibitors, we discuss how better understanding the pharmacologic basis for these effects could optimize their use for individual patients.

Keywords

Angiogenesis; Sunitinib; Sorafenib; Bevacizumab

As of December 2008, five agents described as angiogenesis inhibitors—bevacizumab, lenalidomide, sorafenib, sunitinib, and thalidomide—have been approved for marketing by multiple national and continental regulatory agencies for the treatment of cancer. Several more agents—axitinib (AG013736), cediranib (AZD2171), motesanib (AMG706), vandetanib (ZD6474), and aflibercept (VEGF-Trap)—are in advanced stages of clinical development. Extensive preclinical research and several clinical trials have supported the use of this drug class in cancer therapy, but findings from human clinical trials and broader use of these agents have reduced the initial expectations for this new class of drugs [1, 2]. Although these drugs have prolonged survival and become standard of care for patients with some advanced, incurable diseases, long-term disease stabilization is achieved in few [3–5]. Meanwhile, a growing list of unexpected and sometimes severe adverse events [6–14] have led some investigators to call for more intensive study of the mechanisms of these effects and better methods to manage and prevent their complications [15, 16].

For nearly 40 years, the physiologic process of angiogenesis has been recognized as a target for anticancer therapy [17]. Defined as the generation of new branches from pre-existing blood vessels, this process is critical for the development, subsequent growth, and metastasis of tumors. The original rationale for angiogenesis as a target for anticancer therapy derived from comparing the rapid rate of endothelial cell growth necessary to support the growth of

Correspondence to: Michael L. Maitland, mmaitlan@medicine.bsd.uchicago.edu.

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the adjoining tumor relative to the near quiescence of endothelial cells of the normal adult vasculature. This ratio of sensitivity of the tumor vasculature to normal vasculature for disruption of endothelial cell growth offered a therapeutic index within which drugs could safely and effectively limit tumor growth and metastasis [19, 20].

A monoclonal antibody that bound the vascular endothelial growth factor (VEGF) molecule was one of the first antiangiogenic agents to demonstrate control of tumor growth in mice [21]. VEGF is the ligand in a signaling pathway crucial for endothelial cell function, proliferation, and survival under stress. It triggers these downstream effects primarily by binding and activating its cognate receptor: VEGF-receptor 2 (VEGFR2) encoded by the kinase insert domain receptor (*Kdr*) gene (Fig. 1). Bevacizumab, a humanized monoclonal antibody specifically binds VEGF, while the small molecules sorafenib and sunitinib bind and inhibit several kinases important to downstream signaling from VEGF including VEGFR2. As the primary mechanism by which these agents mediate their antiangiogenic effects is through the same signaling pathway, it might be useful to refer to bevacizumab, sorafenib, sunitinib, and the as yet commercially unavailable agents aflibercept, axitinib, cediranib, motesanib, and vandetanib collectively as VEGF-signaling pathway (VSP) inhibitors.

VEGF signaling is important to angiogenesis, which comprises not just endothelial cells, but a complex process of tissues. To branch new blood vessels from pre-existing ones includes degradation of the vessel basement membrane, migration, growth, and division of endothelial cells and pericytes, and influx and differentiation of endothelial cell precursors derived from the bone marrow, with the synthesis of new basement membrane, and formation of intercellular junctions [22] (Fig. 2). These cells, leukocytes, platelets, and even the surrounding acellular matrix of glycoproteins produce or display a variety of molecules important to this dynamic process. Interventions that inhibit any or several steps might be considered “antiangiogenic.” For example, in addition to the agents described above, the taxanes, sub-maximally tolerated doses of various chemotherapies, and even radiation have been declared “antiangiogenic” [23]. Hence classifying drugs as angiogenesis inhibitors is non-specific and interferes with our capacity to appreciate fundamental differences in their pharmacology. For example, thalidomide and its metabolites have diverse effects on inflammatory, endothelial, and tumor cells. The second-generation immunomodulatory agent with similar structure, lenalidomide, has 50,000-fold increased potency for tumor necrosis factor alpha (TNF-α) signaling inhibition, but the degree to which it better inhibits angiogenesis remains undetermined [24]. These drugs inhibit angiogenesis in various standardized assays, and the molecular mechanism appears to be via effects on endothelial cell phospholipids [25].

During the course of clinical development of the VSP inhibitors, the concept of the therapeutic index for tumor versus normal vasculature disruption has commonly been simplified to the point of implying that angiogenesis in the healthy adult only occurs in wound healing, and ovarian and endometrial proliferation [26]. Consistent with this perspective was an expectation that VSP inhibitors could have dramatic effects as monotherapy and experiments in animal models confirmed this hypothesis [27–30]. However, at tolerable doses the VSP inhibitor bevacizumab has had modest single agent activity against solid tumors [31–33] in human patients, and further development of this agent has favored a combination treatment approach [5, 34–37]. Although sorafenib and sunitinib have had single agent activity in multiple solid tumors, the extent of this activity is likely due to inhibition of kinases not only important to angiogenesis but to other tumor growth-related processes as well [13, 38, 39]. Some dose-limiting toxicities of these agents have been due to effects on the systemic vasculature. Of these, the most common has been

hypertension, but the extent to which other non-specific complaints—fatigue, headache, abdominal pain—also might be attributed to vascular effects is unclear.

VSP inhibition is clearly a useful new method for treating tumors, having already proved to extend survival in patients with renal cell [3], colorectal [36], hepatocellular [39], and non-small lung carcinomas [5]. The three agents currently approved for marketing in the United States—bevacizumab (Avastin™), sorafenib (Nexavar™), and sunitinib (Sutent™)—are also being studied in combination with many standard treatments in a variety of cancers and in adjuvant therapy for curable early stage disease. However, VSP inhibition is only one mechanism by which to disrupt tumor angiogenesis. To fulfill Folkman's original vision for exploiting the therapeutic index of targeting the process of tumor angiogenesis will not only require the development of alternative antiangiogenic agents, but also a better evaluation of the therapeutic index specific for the VSP inhibitors.

The initial development of any new drug or class of drugs in oncology entails a first approximation of dosing, scheduling, and supportive care sufficient for a cohort of patients with a given disease to benefit convincingly from the addition of the new agent(s) to standard care. In subsequent efforts better characterizing the therapeutic index can lead to better safety and consequently expanded indications for the class. For the VSP inhibitors this characterization requires: 1) determining which adverse events are mechanism-independent ("off-target") and which are mechanism-dependent (target-related); 2) determining the relationship between drug dose and exposure, mechanism-dependent effects, and therapeutic effects; and 3) based on these findings refinement and testing of the originally determined general patient selection, drug selection, drug dosing, and approaches to supportive management. As an example of how this characterization can lead to better use of VSP inhibitors we first review cardiovascular toxicities of VSP inhibitors: elevation in blood pressure, left-ventricular dysfunction, and bleeding/thrombosis. We then discuss how prediction, early recognition and effective management of these events and understanding the relationship of these adverse effects to drug administration might improve clinical outcomes for patients treated with these agents.

Cardiovascular toxicities of VSP inhibitors: hypertension, ventricular dysfunction, and bleeding/thrombosis

Hypertension

Clinical data alone support the contention that hypertension is a mechanism-dependent, or mechanism-based, toxicity of VSP inhibition. Prior to the successful development of VSP inhibitors, VSP agonists were tested in clinical trials to induce angiogenesis in ischemic cardiomyopathy [40] and the infusion rate-limiting toxicity was hypotension. All inhibitors of the VSP have been demonstrated to cause hypertension in some fraction of patients receiving them [41]. A newer agent, CDP-791, with greater specificity for signaling through VEGFR2, causes hypertension in some patients [42]. Hypertension is a categorical toxicity, and blood pressure elevation is the measurable, mechanism-based effect of VSP inhibition. Multiple studies have demonstrated that the mean blood pressure for a cohort of patients receiving VSP inhibitor therapy increases even among patients who do not develop hypertension [43–45].

There is supportive evidence for two putative mechanisms by which VSP inhibition leads to blood pressure elevation: 1) acute disruption of vasodilator production leading to arteriolar vasoconstriction, and 2) chronic depletion of microvascular endothelial cells leading to a net reduction in normal tissue microvessel density, a process called rarefaction. The evidence for diminished vasodilator production is indirect. The endothelial nitric oxide synthase enzyme (NOS III) is post-translationally activated by the VSP (Fig. 1) and this is the

mechanistic basis for recombinant VEGF causing acute hypotension [46]. Studies of bevacizumab, incubated with human umbilical vein endothelial cells, demonstrate reduction in nitric oxide production within hours of incubation [47]. In rodents, the administration of VEGFR2 inhibitors leads to morphologic evidence of vasoconstriction, but this is additive with pharmacologic inhibitors of nitric oxide synthase, suggesting that VSP inhibition might cause acute microvascular vasoconstriction by mechanisms independent of NOS III activation [48]. Regardless, one prospective human subject study of repeated blood pressure measurements throughout the first-day of exposure to sorafenib demonstrated that blood pressure elevation can be detected within the first 24 h of exposure to a VSP inhibitor [49]. Most of the blood pressure elevation occurs during this time frame although there is a further measurable increase until steady state plasma drug concentrations are reached and blood pressure plateaus thereafter (even in patients who do not develop hypertension and do not require antihypertensive therapy). Most studies of VSP inhibitor-induced blood pressure elevations have measured blood pressure and microvascular rarefaction at later time points. Regardless of the specific VSP inhibitor tested, these studies [44, 45, 50] consistently demonstrate vascular physiologic measurements and in one case, tissue samples [45], reflecting rarefaction. Detailed morphologic characterization of these microvascular changes and their reversibility has been captured in rodent models [51].

The effects on blood pressure, secondary to the direct changes to capillary function and structure, reflect the important role VEGF signaling plays in the maintenance of the non-tumor microvasculature. Imaging experiments in rodents suggest that the effects of VSP inhibition are rapid and reversible [52] and more consequential to the vasculature of younger than older animals [53]. The human subject studies described in the previous paragraph have arguably confirmed that changes in blood pressure have parallel rapidity and reversibility in humans treated with VSP inhibitors, but the role of age on the sensitivity of the normal human vasculature to VSP inhibitors remains unconfirmed. The relationship between normal vasculature sensitivity to VSP inhibition and tumor vasculature sensitivity to VSP inhibition also is undetermined.

There is no doubt that the diversity of human blood pressure regulatory and counter-regulatory mechanisms presents a challenge for the interpretation of blood pressure data as a biomarker for the effects of VSP inhibitors on the tumor vasculature. However, given: 1) the vast base of knowledge on the limits and value of different forms of blood pressure measurement as a biomarker for cardiovascular disease, 2) the temporal association of changes in blood pressure with exposure to VSP inhibitors, and 3) the mechanistic relationship among VSP inhibition effects on blood pressure, specific elements of microvasculature regulation, and angiogenesis suggest that blood pressure is a probably valid biomarker for the pharmacodynamic effects of VSP inhibitors. How this mechanism-based effect can be used to optimize administration of VSP inhibitors will be discussed in the section, “Optimizing Administration.”

Ventricular dysfunction

The afterload stress presented by VSP-inhibitor-induced blood pressure elevations might play a role in the pathogenesis of the ventricular dysfunction associated with sorafenib and sunitinib, but it does not appear that the disruption of VEGF signaling directly results in ventricular dysfunction. This toxicity has not been associated with bevacizumab, but has been reported in studies of the kinase inhibitors sorafenib and sunitinib, and the non-VSP kinase inhibitor imatinib. These agents overlap in their disruption of signaling by the platelet derived growth factor receptor (PDGFR), c-Kit and, to a lesser extent, c-Abl. Detailed study, first of rodent models [54], then of chemical modifications of imatinib [55], demonstrated that the disruption of Abl signaling increases the likelihood for cardiac myocytes to undergo apoptosis and is an important factor in kinase inhibitor-induced ventricular dysfunction. In

addition, Khakoo et al. [56] have suggested that PDGFR plays a protective role in ventricular remodeling in response to stress as recombinant PDGF has been shown in animal models to be of therapeutic benefit in heart failure [57]. These investigators have proposed a "one-two punch" hypothesis in which the first hit is the elevation of systolic blood pressure through VSP inhibition, which increases afterload, and the second hit is the blockage of PDGFR signaling, which through the cardiac myocyte impairment in response to stress causes ventricular dysfunction. Force et al. [58] have suggested that multiple inhibitory activities are at play, and that angiogenesis is necessary for ventricular remodeling in response to afterload stress. Hence, while disruption of the VSP might play a role in VEGFR2-inhibitor-mediated heart failure, this adverse event appears to be a mechanism-independent (or "off-target") effect of some VSP inhibitors.

The incidence of ventricular dysfunction due to sunitinib and the clinical significance of these changes remain unclear. Until recently, all reports were either case series or retrospective analyses reporting a broad range of frequencies. Motzer et al. were the first to report the association between the use of sunitinib and decline in left ventricular ejection fraction. Their phase III study of sunitinib versus interferon alpha in patients with previously untreated metastatic renal cell carcinoma [4] reported a 10% incidence of decline in left ventricular ejection fraction to below normal and there was a significantly increased number of patients with this cardiotoxicity in the sunitinib arm compared to the interferon-alpha-arm. In this study, however, there were no reported clinical sequelae and after discontinuation or dose modification, all cardiac dysfunction reversed. Although this study suggested that most cardiac dysfunction was reversible and clinically insignificant, this contrasted with a small, single institution, retrospective chart review by Telli et al. [59] in which they found 7/48 patients with evidence of clinically significant changes in left ventricular function. Chu et al. [60] conducted a retrospective study of patients treated with sunitinib and found that 2/36 patients with apparently normal pre-treatment cardiac function had a decline in left ventricular ejection fraction of at least 20% and 7/36 with a decline of at least 15%, and 4 patients developed the clinical syndrome of congestive heart failure. Although patients with a history of cardiac events were enrolled, all were asymptomatic and had a baseline ejection fraction of 50% or greater prior to treatment. A prospective study of the effects of sorafenib on left ventricular ejection fraction measured by serial multiple gated acquisition scan (MUGA) imaging in 24 patients detected no significant declines in the mean ejection fraction for the cohort between baseline and 5 cycles of treatment. Two patients had their ejection fractions decline by more than 10% [61]. In the only published prospective study to date of cardiac toxicities in patients with metastatic renal cell carcinoma who received sorafenib or sunitinib, 25/74 experienced a cardiac event [62]. Their protocol defined cardiac event as: the occurrence of increased cardiac enzymes if normal at baseline, symptomatic arrhythmia that required treatment, new left ventricular dysfunction, or acute coronary syndrome. Of these 25 patients, 13 were symptomatic and 7 required intermediate care and/or intensive care admission. Although the measurements were not provided, 9/25 subjects having a cardiac event had measurable declines in left ventricular ejection fraction. Finally, retrospective chart analysis of 224 patients who were prescribed sunitinib during one year at M.D. Anderson Cancer Center revealed 6 patients who prior to sunitinib treatment had no symptoms of heart failure and developed symptomatic heart failure within 44 days of initiating sunitinib. One patient died from apparent cardiac complications, 2 had VSP inhibitor therapy discontinued, 1 successfully remained on sunitinib therapy but with later recurrence of heart failure, 1 switched from sunitinib to sorafenib after initiation of supportive management without further deterioration in cardiac function. Collectively, these data indicate: 1) ventricular dysfunction is associated with exposure to the VEGFR2 kinase inhibitors (bevacizumab does not appear to have these effects, but comprehensive studies have not been published), 2) there are complex, interrelated mechanisms of heart failure linked to inhibition of specific kinases important to myocyte responses to pressure loads, 3)

the clinical significance of VSP-inhibitor-induced heart failure is variable, with some patients having been able to return to treatment with aggressive supportive care and though a small fraction of a cohort of patients with high cancer mortality, some died, in part, from cardiac complications.

Bleeding and thrombosis: vascular toxicities of VSP inhibitors

Bleeding and thrombosis have been associated with the use of VSP inhibitors. Bleeding events include ecchymoses, epistaxis, hemoptysis, wound site bleeding, and menorrhagia. Most of these events are uncomplicated and improve with supportive management or temporary cessation of VSP inhibitor therapy. Fatal pulmonary hemorrhage has occurred with squamous cell lung cancer patients receiving any of the VSP inhibitors [12, 13, 63]. In the registrational trials for each agent, bleeding events were reported to be associated with treatment [3, 36, 38]. Initially, VSP inhibition was associated primarily with arterial thrombotic events only [64], but subsequent meta-analysis suggests a marginally increased risk for venous thromboembolism as well [65]. Others have published detailed discussion of specific mediators and putative mechanisms for these effects of VSP inhibitors [41, 66, 67]. The primary concept is that within the microvasculature, where VSP inhibitors have their predominant effects, there is a fine balance of pro- and anticoagulant proteins, platelet-activating and inhibiting molecules, and pro- and antifibrinolytic products all acting to maintain vessel integrity and intravascular flow [66]. Depending on the nascent state of these vessels and proximity of the tumor to larger vessels, disruption of endothelial function might tip the balance in either direction. There might be more specific mechanistic relationships between VSP inhibition, bleeding, and thrombosis, but these have not yet been described. Consequently, at this time, it appears that bleeding and thrombosis are general consequences of angiogenesis inhibition and anti-tumor activity rather than specific molecular consequences of VSP inhibition.

Contrasting cardiovascular toxicities

Characterizing toxicities of new classes of drugs is the first step toward optimizing dose adjustments and supportive care. For all of these cardiovascular toxicities, determination of risk factors is in the earliest stages [60, 62, 65, 68, 69]. As general principles: bleeding and thrombosis are uncommon and appear to be downstream consequences of angiogenesis inhibition and not specific to the VSP inhibitors; ventricular dysfunction is a mechanism-independent effect of these agents; and blood pressure elevation is a mechanism-dependent effect. In all cases the supportive care plan can be focused through pre-treatment risk assessment, appropriate intensity monitoring and evidence-based intervention. The use of these agents however has outpaced development of supportive care methods. For the downstream and off-target effects of bleeding, thrombosis and heart failure: the focus of future research should be on preventive and restorative methods. Additionally, in cases where risk for these consequences is unusually high, patients might be directed to alternative therapies. For the mechanism-based effect of blood pressure elevation, different strategies described below should apply.

Optimizing administration

Two relatively large studies of VSP inhibitors added to standard cytotoxic therapy analyzed the relationship between clear development of hypertension and treatment outcome. Schneider et al. [70] performed a retrospective analysis of the ECOG 2100 trial of paclitaxel with or without added bevacizumab in metastatic breast cancer. In addition to the association of *VEGF* and *KDR* genetic polymorphisms with outcomes, they also assessed, for the patients in the bevacizumab arm, overall survival among the 52 patients who developed grade 3 hypertension (a blood pressure that was higher than 150/100 mmHg and

required more than one antihypertensive agent to get the blood pressure controlled) or grade 4 hypertension (blood pressure elevation associated with life threatening consequences) and the 293 patients who did not develop these grades of hypertension. The median overall survival for the patients who developed grade 3 or 4 hypertension was superior to those who did not develop at least grade 3 hypertension (38.7 *v* 25.3 months, respectively; by Cox proportional hazards model p=0.002). A similar relationship was demonstrated for patients with pancreas cancer in an open-label randomized phase II trial of gemcitabine and the oral VSP inhibitor axitinib. Among 61 patients assigned to receive gemcitabine and axitinib, at some point in the trial 27 developed a diastolic blood pressure ≥90 mmHg, and 34 had no such documented measurement. This measure would correspond to any grade 2 or 3 hypertension. In this post hoc, exploratory analysis, the investigators found the median overall survival for the 27 subjects who ever had a diastolic blood pressure at least 90 mmHg to be 13 months [95% confidence interval 8.5, 16.6] and for 34 subjects with no measurements greater than 89 mmHg it was 5.6 [4.8, 7.2]. Although post-hoc analyses, these data suggest that VSP inhibition effects on blood pressure are associated with the therapeutic benefit of these drugs, regardless of the disease being treated or the accompanying agent.

If we accept that blood pressure elevation is a mechanism-based effect of VSP inhibitors, and if the addition of a VSP inhibitor to standard treatment has a survival benefit, then these results should be valid, reproducible, and no surprise. What is the difference between the population of patients who developed blood pressure elevations and those who did not? Most simply we can say that with few exceptions, all subjects in the populations with higher blood pressure had clearly received sufficient dosing of either axitinib or bevacizumab to have the therapeutic effect. All subjects for whom the administered treatment was insufficient for the therapeutic benefit or who were particularly resistant to the effects of the treatment on their microvasculature were in the DBP <90 mmHg or “no grade 3 or 4 hypertension” populations. Consequently, one would expect that—regardless of the quantitative relationship between VSP inhibition, blood pressure elevations, and beneficial changes to tumor vasculature—there will be a difference in the survival of populations receiving sufficient doses of therapy to detect a mechanism-based effect and a population of patients in which some might have received insufficient treatment.

These data confirm the hypothesis that blood pressure elevation is a mechanism-based effect of VSP inhibitors and suggest that more careful evaluation of blood pressure might benefit patients receiving these drugs. The best approach to individualizing VSP inhibitor dosing is still unclear, but the answer *is not* to dose patients until they develop hypertension. This approach would likely lead to more frequent and severe adverse events. Instead, studies that better characterize the dose/exposure/change-in-blood pressure relationship might be useful. At some point the negative consequences of hypertension on the systemic vasculature might become more life threatening than the cancer being treated. In one study of rodents receiving the VSP inhibitor cediranib, initiation of ACE inhibitor therapy with administration of cediranib had no detectable effects on the anti-tumor activity of cediranib [71]. This finding suggests that the microvascular changes caused by VSP inhibition (that are reflected by blood pressure elevation) and not the blood pressure elevation itself are necessary and sufficient for therapeutic effect.

As blood pressure is a mechanism-based effect of VSP inhibition that increasingly appears to be a pharmacodynamic marker for the therapeutic effect of VSP inhibition, how should the cancer research and treatment communities proceed to use this information to optimize administration?

1. Better measurement: Blood pressure varies within individuals over the course of the day and nonstandardized methods of measurement typically used in clinicians’ offices produce additional variability to this measurement [72–74]. Consequently,

the individual's measurements over time are difficult to interpret without more rigorous methods. To overcome this challenge, our group has implemented ambulatory blood pressure monitoring in our pharmacologic studies of VSP inhibitors. Ambulatory monitoring devices collect more than 40 measurements over a 12–24 h interval. By increasing the number of measurements collected across different times of day and different levels of activity and determining a mean blood pressure from these measurements a more accurate and reproducible value is generated. Mean ambulatory blood pressure resists many of the external factors that account for placebo effects in antihypertensive drug trials [73]. It is recognized that this is currently an impractical method for oncologists treating cancer patients with VSP inhibitors, but more careful measurement, attentive to proper cuff sizing, patient positioning, and comprising multiple rather than a single measurement during an office visit, as recommended for primary care physicians [74], should improve the sensitivity for the clinician to detect potentially dangerous blood pressure elevations in their patients.

2. Not dosing to toxicity or managing prophylactically: As mechanism-based toxicities of new anti-cancer drugs have been identified, some have taken a maximum-dose approach to using these mechanism-based toxicities as pharmacodynamic biomarkers without understanding the dose/response relationship [75]. In advanced cancer patients without alternative options, this is not an unreasonable approach, but it does run the risk of causing excess toxicity without any therapeutic benefit. As the consequences of acute, severe, hypertension would be greater than severe rash, this would not be an acceptable approach with VSP inhibitors. The rodent data from Curwen et al. [71] suggest an approach where dose might be escalated in the setting of careful management of hypertension with appropriate antihypertensive agents and one such study is ongoing (NCT00436579, http://www.cancer.gov/search/ViewClinicalTrials.aspx) to determine whether escalation to blood pressure effect is safe and feasible.

3. Biomarker discovery: As noted, blood pressure is a validated, qualified biomarker for cardiovascular disease and though there are limitations to its use in clinical practice, these known limitations are helpful in the investigational setting. If blood pressure should prove not to be a pharmacodynamic biomarker useful in the clinical setting, it might be used in methods to discover novel biomarkers, for example laboratory tests, that might document the effects of VSP inhibitors on the systemic vasculature more reproducibly.

Future directions

These cardiovascular toxicities have been identified primarily in advanced cancer patients who have received VSP inhibitor therapy for short periods. Under these conditions, these toxicities have typically been manageable. However, these patients have relatively short life expectancies and so the surveillance infrastructure for cardiovascular adverse events (elevated blood pressure, peripheral edema, dyspnea, etc.) is more lenient than the general medical community for detecting and managing these complications. Therefore, retrospective analysis has provided just a limited signal of what is likely on more careful prospective testing to be clinically significant adverse effects in patients with better long-term prognoses [69, 76]. To enable the greatest number of patients to receive the full benefits of these important new classes of anticancer drugs will require methods of better risk stratification, adverse effect detection and management, as we have developed for neutropenia/fever, and nausea/emesis. In the short term this might best be achieved for individual patients by oncologists through close collaboration with colleagues in general internal medicine and cardiovascular specialties [15, 76, 77]. At the population level,

consensus recommendations from expert, independent, interdisciplinary panels might be preferable to individual expert opinion, empiricism, and individual, corporate-prepared guidance for individual drugs. In the longer term, prospective studies testing the most clinically relevant and pragmatic approaches are needed. Although these toxicities are concerning, measurement of sub-toxic effects and understanding their mechanisms provides an opportunity for VEGF-signaling pathway inhibition to fulfill its promise as a strategy not just for treating, but also curing cancer.

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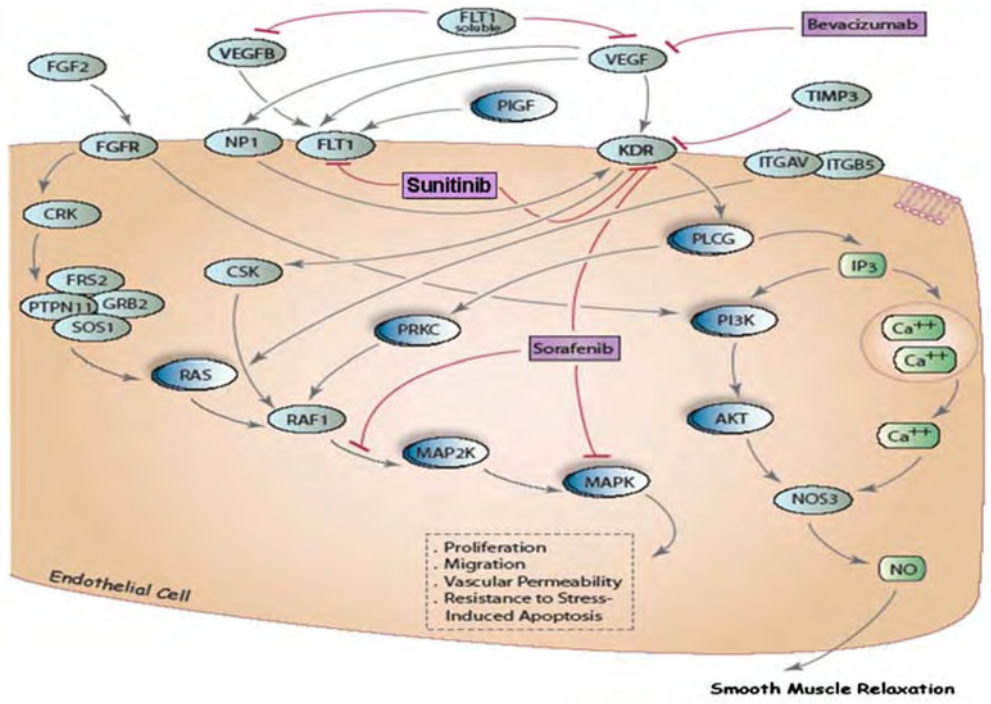

Fig. 1.

The VEGF Signaling Pathway within endothelial cells. Each circle depicts a different protein represented by its respective gene abbreviation with activation of the next protein represented by arrows and inhibition by flat lines. The rectangles depict the primary mechanism[s] of action on endothelial cell signaling by each drug. The curved boxes depict phosphatidyl inositol triphosphate (IP_3), calcium (Ca^{++}), and nitric oxide (NO). The diagram is modified and reproduced with permission from PharmGKB (Klein TE, Chang JT, Cho MK, Easton KL, Fergerson R, Hewett M, Lin Z, Liu Y, Liu S, Oliver DE, Rubin DL, Shafa F, Stuart JM, Altman RB (2001) Integrating genotype and phenotype information: an overview of the pharmGKB project.Pharmacogenomics Journal 1:167–170)

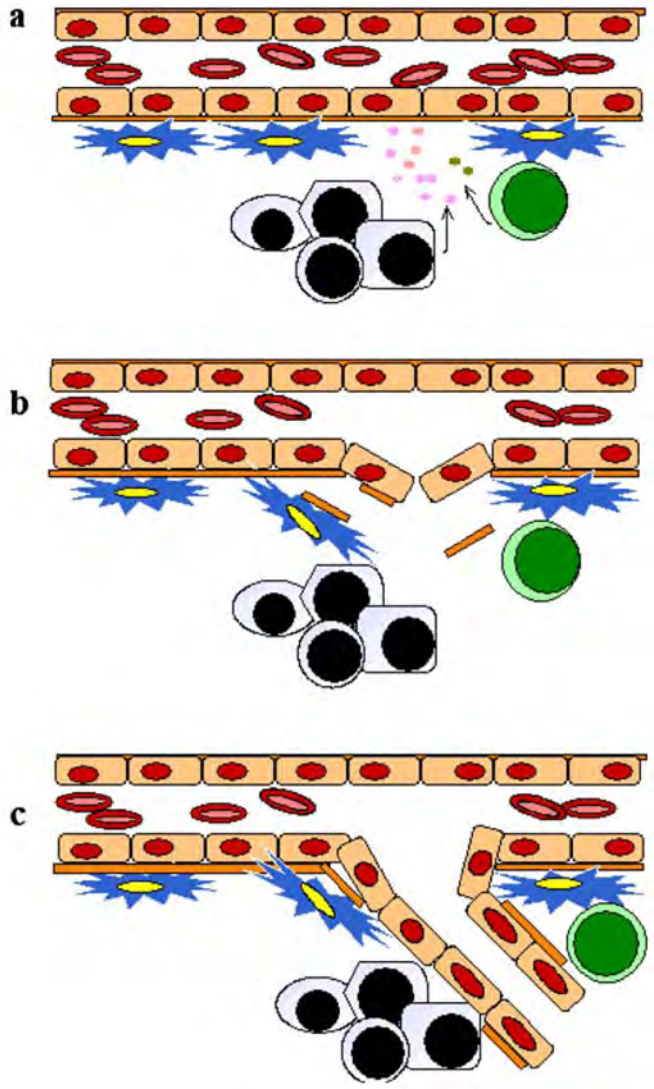

Fig. 2.

Angiogenesis is a stepwise, multi-cellular process. **a** Initiation of angiogenesis by a cluster of tumor cells (grey) producing vascular endothelial growth factor (dots) and a tissue monocyte producing cytokines and enzymes contributing to the process on an intact capillary. In the intact vessel, endothelial cells (orange cytoplasm/red nuclei) are constrained by a basement membrane (long bars) and supported by pericytes (star-shaped nuclei). **b** These factors lead to breakdown of the basement membrane, endothelial cell detachment from the basement membrane and migration, and reduced pericyte support for the structure. **c** Through migration and division, endothelial cells form a new branch to the preexisting vessel. The new branch has diminished structural integrity (reduced basement membrane contacts, and reduced pericyte coverage leading to a leakier vessel)