Noncardiac Vascular Toxicities of Vascular Endothelial Growth Factor Inhibitors in Advanced Cancer: A Review

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ABSTRACT

Summary. The introduction of molecularly targeted anticancer therapies has brought the promise of longer survival times for select patients with cancers previously considered untreatable. However, it has also brought new toxicities that require understanding and management, sometimes for long periods of time. Vascular endothelial growth factor inhibitors are associated with a broad range of adverse effects, with vascular toxicity being particularly serious. This review focuses on the current understanding of the pathophysiology and mechanisms of macrovascular toxicities (hypertension, hemorrhage, and thromboembolism), their incidence and severity, the current clinical management, and implications in the advanced cancer setting. Movement of these agents into

the early disease setting will alter the impact of these toxicities.

Search Strategy and Selection Criteria. Information for this review was collected by searching PubMed/Medline and American Society of Clinical Oncology abstract databases. The medical subject heading terms used included toxicity, hypertension, thromboembolism, hemorrhage, intestinal perforation, risk factors, pharmacokinetics, and metabolism, combined with free text search terms including, but not limited to, VEGF inhibitor*, bevacizumab, sunitinib, and sorafenib. Articles published in English before March 2010 were included, in addition to information from case reports and pharmaceutical agent package inserts. *The Oncologist* 2011;16:432–444

INTRODUCTION

Chemotherapy for cancer is associated with a range of unwanted toxicities including, for example, emesis [1], cyto-

penias [2], mucositis [3], cardiac and skin toxicities [4], and many others. With the introduction of targeted anticancer therapies (TATs), new toxicities have evolved requiring

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new management strategies. TATs act on specific molecular pathways involved in various stages of carcinogenesis, and ideally the target pathways and receptors would exist only on malignant cells [5]. However, receptors are present on normal cells in heart muscle, skin, and vascular tissue, leading to significant toxicities at these sites [3]. The nature of the pathways affected has led to a new range of toxicities that clinicians are only beginning to understand. Because the mechanism of toxicity is commonly the mechanism of action of the drug, reducing toxicity without abolishing the antitumor effect poses a real challenge.

Vascular endothelial growth factor (VEGF) is a key mediator in the regulation of angiogenesis. Interaction between VEGF isoforms and their receptors induces signaling that leads to endothelial survival, which is inhibited by VEGF inhibitors (VEGFI) (Fig. 1). VEGF is important in normal developmental physiology and in tumor development [6], but is considered to have a limited role in adults, making it an ideal target for tumor treatment [6]. VEGF inhibits apoptosis and raises tumor interstitial pressure, decreasing the likelihood of cytotoxic drugs entering tumor cells [7]. It is a vasodilator, and has somewhat predictable effects on the vascular system [8]. Greater VEGF expression correlates with greater tumor invasiveness, vascular density, metastatic ability, and tumor recurrence [9]. The current most commonly used VEGFIs are the monoclonal antibody (mAb) bevacizumab and the small molecules sunitinib and sorafenib, although new drugs are being licensed constantly.

Bevacizumab is a humanized mAb to VEGF and was the first antiangiogenic agent approved as first-line therapy for metastatic colorectal cancer (mCRC) [9]. It acts by preventing binding of VEGF to its receptors, thereby inhibiting the signaling process [2], leading to an imbalance in the angiogenesis pathway, and preventing tumor angiogenesis, thus increasing the delivery of chemotherapy to tumor cells [10]. It is currently used in conjunction with chemotherapy in patients with mCRC as both first- and second-line therapy [9, 11], and was recently approved for use in patients with metastatic renal cell carcinoma (mRCC), metastatic human epidermal growth factor receptor 2–negative breast cancer, glioblastoma multiforme, and non-small cell lung carcinoma (NSCLC) [12–15]. Toxicities include hypertension, proteinuria, hemorrhage, and gastrointestinal (GI) complications [3]. More than 200,000 patients have been treated with bevacizumab and the toxicities are mostly mild to moderate [10].

Sunitinib and sorafenib are pleiotropic small molecule tyrosine kinase inhibitors (SMTKIs) that target VEGF receptor (VEGFR), in addition to platelet-derived growth factor receptor, Flt-3, Ret, Kit, Raf, and colony-stimulating

factor 1 receptor, among others. They are currently U.S. Food and Drug Administration (FDA) approved for use in a number of advanced cancers including RCC, hepatocellular carcinoma (HCC), and gastrointestinal stromal tumors (GISTs) [16–19]. Pazopanib is the latest SMTKI to be FDA approved for the treatment of RCC [20]. Many more agents are under investigation in clinical trials (Table 1) and we are likely to witness an explosion of newly approved agents in the coming years.

MACROVASCULAR TOXICITIES OF VEGFIS

The major noncardiac vascular toxicities of VEGFIs are hypertension, hemorrhage, perforation, and thromboembolism. Grading using the National Cancer Institute Common Toxicity Criteria of Adverse Events (NCI-CTCAE), version 4.0 and version 3.0 is shown in Table 2. An overview of frequency, monitoring, and intervention is shown in Tables 3 and 4.

Hypertension

Hypertension is one of the most frequently described adverse effects of VEGFI therapy. Uncontrolled high-grade hypertension can lead to serious consequences, including myocardial infarction, cerebrovascular accident, renovascular disease, and arteriosclerosis [21]. Treatment-induced hypertension is dose dependent and reflects on-target inhibition rather than off-target effects (Fig. 2), because it is closely correlated with the potency of VEGFR-2 inhibition [22]. SMTKIs such as cediranib and axitinib, which inhibit VEGFR-2 at lower concentrations, lead to a higher rate of hypertension than with sorafenib and sunitinib, which bind to other targets with greater affinity [22]. In fact, in early studies with sorafenib, hand–foot syndrome and diarrhea were the dose-limiting toxicities (DLTs) for sorafenib without significant hypertension, whereas with cediranib and axitinib, hypertension was the DLT. A recent pharmacokinetic/pharmacodynamic meta-analysis by Houk et al. [23] identified a positive relationship between diastolic blood pressure changes and total sunitinib (and its metabolite SU12662) exposure, but this has not been confirmed for other agents such as axitinib [24], and further studies are warranted.

Bevacizumab is also associated with the development or worsening of hypertension [25]. In combination with sunitinib or sorafenib, bevacizumab causes earlier onset, more frequent, and more severe hypertension than with single agents [26]. The frequency of all grades of hypertension associated with VEGF inhibition is 20%–30% with bevacizumab and 15%–60% with SMTKIs [27]. The incidence of hypertension could well be underestimated because of the different classifications and definitions used among the different trials and infrequent

Figure 1. VEGF signaling is required for endothelial cell survival. VEGFIs target VEGF cell surface receptors (monoclonal antibodies) and intracellular pathways (small molecule tyrosine kinase inhibitors), resulting in the inhibition of endothelial cell survival, proliferation, and migration, thereby inhibiting angiogenesis.

Abbreviations: VEGF, vascular endothelial growth factor; VEGFI, VEGF inhibitor; VEGFR, VEGF receptor.

blood pressure measurements in the outpatient setting [28]. With SMTKIs, the incidence of hypertension may also vary according to tumor type, being higher in RCC than in HCC (sorafenib) and GIST (sunitinib) patients. A proportion of patients in mRCC trials may have undergone nephrectomy, which gives a higher risk for hypertension, either from hypervolemia [29] or from underlying pre-existing renal disease [30]. On the other hand, patients with HCC may already be on β -blockers, and/or diuretics for portal hypertension and this may mask the true incidence of hypertension. Established VEGFI toxicity risk factors are a history of hypertension and coronary heart disease [31]. Race (worse in African-Americans) and age (worse for those aged >75 years) have also been suggested. Pharmacogenetic toxicity studies may provide insights into interpatient variation [32]. It was recently suggested

that hypertension is related to longer survival with axitinib, sunitinib, bevacizumab [33], and tivozanib. As such, hypertension may act as a biomarker of early activity of VEGFIs.

Pathogenesis

VEGF is a known vasodilator, so vasoconstriction is an expected consequence of VEGF inhibition, although the exact pathophysiology of VEGFI-induced hypertension is not entirely understood. A number of hypotheses have been proposed. Endothelial dysfunction is considered to be a direct effect of VEGF signaling inhibition. VEGF upregulates endothelial nitric oxide synthase and prostacyclin, leading to nitric oxide (NO) production via the phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase pathways [34]. Inhibition of VEGF signaling could lead to a decrease in NO and

Table 1. VEGF inhibitors for cancer treatment

Name	Trade name	Research name	Targets
Bevacizumab	Avastin®		VEGF
Ramucirumab		IMC 1121B	VEGFR-2
Aflibercept	VEGF Trap®	AVE0005	VEGF
Sunitinib	Sutent®	SU11248	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β Kit, Ret, CSF-1R, Flt-3
Sorafenib	Nexavar®	BAY-43-9006	VEGFR-2, VEGFR-3, Raf, B-Raf, Kit, Flt-3, PDGFR- β
Vatalanib		PTK787/ZK 222584	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , Kit, FMS
Vandetanib	Zactima®	AZD6474	VEGFR-2, EGFR, Ret
Cediranib	Recentin®	AZD2171	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, Kit
Axitinib		AG-013736	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, Kit
Semaxanib		SU5416	VEGFR-1, VEGFR-2, PDGFR, Kit
Pazopanib	Votrient®	GW786034	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , Kit
Motesanib		AMG 706	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, Kit
Telatinib		BAY 57-9352	VEGFR-2, VEGFR-3, PDGFR, Kit
Tivozanib		AV-951	VEGFR-1, VEGFR-2, VEGFR-3
		AEE788	VEGFR-2, EGFR, HER-2
Foretinib		GSK1363089	VEGFR-2, c-Met, HGF

Abbreviations: CSF-1R, colony-stimulating factor 1 receptor; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2; HGF, hemopoietic growth factor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor.

prostacyclin activity, altering vasodilatory ability and leading to increased vascular resistance and blood pressure. Another mechanism may be rarefaction, a decrease in arteriole and capillary densities. Although rarefaction is known to be an early event in hypertension, it has yet to be definitively proven as causative [35]. VEGF is known to act in a homeostatic fashion in nonpathogenic conditions and is required for endothelial survival [36]. VEGF inhibition is likely to cause endothelial apoptosis, contributing to rarefaction. Two small studies showed rarefaction in patients treated with telatinib (BAY 57-9352) and bevacizumab [37, 38], indicating that this may be a significant contributor to hypertension in patients treated with VEGFIs. Lastly, increased arterial stiffness within the proximal and distal blood vessels may also contribute to the pathogenesis of hypertension [39]. In patients treated with sorafenib, increased aortic wall stiffness has been a postulated mechanism of hypertension, especially in the absence of underlying renovascular causes or blood volume-related changes [40].

Clinical Manifestations and Management

Hypertension per se is often asymptomatic. However, patients can develop seizures and impaired vision acutely, so the diagnosis of posterior reversible leukoencephalopathy

syndrome (PRES) needs to be considered. This is rare (<1% of patients treated with VEGFI therapy) and has been reported with bevacizumab, sorafenib, sunitinib, and vatalanib [40]. PRES can occur within 24 hours and up to months after VEGF inhibition. Capillary leakage and vasogenic edema of the brain have been implicated and noncontrast magnetic resonance imaging is the key to diagnosis. It is reversible with cessation of the implicated agent, although rarely residual neurological deficits can persist [42].

Another syndrome of hypertension, proteinuria, and features of thrombotic microangiopathy (TMA) has been reported in association with sunitinib, sorafenib, and bevacizumab, either combined or as single agents [34, 42]. The TMA was mostly localized to the kidney without all patients exhibiting thrombocytopenia, hemolytic anemia with schistocytosis, and renal dysfunction [42]. Hypertension with or without proteinuria is a class effect of VEGFI therapy, and renal biopsies are rarely performed in the absence of other systemic signs of TMA. TMA of the kidney may therefore be underdiagnosed. Although TMA is more commonly seen in RCC patients, it has been reported in patients with HCC, bronchoalveolar carcinoma, pancreatic cancer, ovarian cancer, and GISTs [34, 43]. It is unclear why RCC patients have a higher incidence of TMA; how-

Table 2. Grading of macrovascular toxicities with National Cancer Institute Common Toxicity Criteria of Adverse Events V4 versus V3

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertension V4	Prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg)	Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg), medical intervention indicated, recurrent or persistent (≥ 24 hrs), symptomatic increase by >20 mmHg (diastolic) or to $>140/90$ mmHg if previously WNL	Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg), medical intervention indicated, more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis), urgent intervention indicated	Death
Hypertension V3	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to $>150/100$ mmHg if previously WNL, intervention not indicated	Recurrent or persistent (≥ 24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to $>150/100$ mmHg if previously WNL, monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
Hemorrhage V4	Mild, intervention not indicated	Moderate symptoms, medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences, urgent intervention indicated	Death
Hemorrhage V3	Mild, intervention not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy	Life-threatening consequences, major urgent intervention indicated	Death
Thromboembolism V4	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated	Death
Thromboembolism V3		Deep vein thrombosis or cardiac thrombosis, intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis, intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death

Abbreviations: BP, blood pressure; V3, version 3.0; V4, version 4.0; WNL, within normal limits.

ever, the solitary kidney or pre-existing kidney disease could explain it.

Hypertension is an independent risk factor for the onset of cardio- and renovascular disease. In patients with metastatic disease, the goal of blood pressure optimization is to allow continuous and safe administration of VEGFI therapy without the need for dose modification. Although more clinical studies are required to determine the best antihypertensive agent, angiotensin-converting enzyme (ACE) inhibitors are a logical choice because they may also improve underlying proteinuria, especially with bevacizumab [44]. Angiotensin II inhibitors, diuretics, hydroxydipyrindine calcium channel blockers (CCBs), and β -blockers are also possible antihypertensive agents. The nondihydroxydipyrindine CCBs (verapamil and diltiazem) are cytochrome P450 (CYP)3A4 inhibitors so are used cautiously in conjunction with VEGFIs metabolized by the CYP3A4 pathway [44, 45].

Target blood pressure as recommended by the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure is $<140/90$ mmHg. Caution is required especially in the setting of GI toxicity, wherein hypotension, dehydration, and renal failure could

be potential adverse outcomes. Furthermore, ACE inhibitors and diuretics could result in renal dysfunction, especially in patients who have undergone nephrectomy. For grade 3 hypertension (Table 4), the implicated VEGFI should be interrupted until the blood pressure is acceptable ($<150/100$ mmHg). Permanent cessation is recommended in grade 4 and uncontrolled grade 3 hypertension. However, rechallenge with the same drug is not unreasonable if blood pressure medications are optimized and the patient is followed extremely closely.

Hemorrhage

Hemorrhage is one of the most severe toxicities associated with VEGFIs [46]. Bevacizumab has the highest frequency of bleeding, and although a pooled analysis of three randomized trials did not demonstrate a significantly higher incidence of grade 3–4 hemorrhage [47], numerous trials have individually reported higher incidences of bleeding [47]. Grade 3–4 hemorrhagic events with bevacizumab occur at a rate of 1.2%–4.6%. However, less severe bleeding occurs in up to 40% of patients [46, 48]. The SMTKIs have so far been associated with a lower rate of bleeding, but events including fatal pulmonary and intracranial hemor-

Table 3. Frequency of VEGFI-induced macrovascular toxicities

Study	Tumor (n)	Agents	Grade ≥ 3 toxicity (%)					
			Hypertension		Hemorrhage		Thromboembolism	
			TAT	C	TAT	C	TAT	C
Escudier et al. (2007a) [81]	mRCC (649)	IFN- α with or without bevacizumab (10 mg/kg)	26 (3)	9 (<1)	33 (3)	9 (<1)	3 (2)	<1 (<1)
Rini et al. (2008) [15]	mRCC (732)	IFN- α with or without bevacizumab (10 mg/kg)	(10)	(0)	(2)	(<1)	(2)	(1)
Sandler et al. (2006) [82]	adv NSCLC (878)	Paclitaxel + carboplatin with or without bevacizumab (15 mg/kg)	(7)	(<1)	(4)	(<1)	NR	NR
Reck et al. (2009) [14]	adv NSCLC (1043)	Cisplatin + gemcitabine with or without bevacizumab (15 mg/kg)	(9)	(2)	(4)	(2)	(7)	(6)
Hurwitz et al. (2004) [9]	mCRC (813)	IFL with or without bevacizumab (5 mg/kg)	22 (11)	8 (2)	(3.1)	(2.5)	(19)	(16)
Giantonio et al. (2007) [11]	mCRC (829)	FOLFOX4 with or without bevacizumab (10 mg/kg)	(6.2)	(1.8)	(3.4)	(0.4)	(3.4)	(2.5)
Llovet et al. (2008) [18]	adv HCC (602)	Sorafenib (bid 400 mg)	5 (2)	2 (1)	7 (1)	4 (1)	NR	NR
Escudier et al. (2007) [17]	adv RCC (903)	Sorafenib (bid 400 mg)	17 (4)	2 (<1)	15 (3)	8 (2)	NR	NR
Motzer et al. (2007) [19]	mRCC (750)	IFN- α with or without sunitinib (qd 50 mg)	24 (8)	1 (1)	12 (1)	1 (0)	NR	NR
Demetri et al. (2006) [16]	adv GIST (312)	Sunitinib (qd 50 mg)	8 (3)	4 (0)	7 (0)	0 (0)	NR	NR
Sternberg et al. (2010) [20]	adv RCC (435)	Pazopanib (qd 800 mg)	40 (4)	10 (<1)	13	5	3	0

Abbreviations: adv, advanced; bid, twice daily; C, control; FOLFOX4, oxaliplatin, leucovorin, and fluorouracil; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; IFL, irinotecan, fluorouracil, and leucovorin; IFN- α ; interferon- α ; mRCC, metastatic RCC; NR, not reported; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; qd, once daily; TAT, targeted anticancer therapy.

rhage have occurred with sorafenib, sunitinib, axitinib, and motesanib [49, 50]. A meta-analysis of 27 trials of sunitinib and sorafenib found that the overall risk for bleeding events was 16.7% for all-grade and 2.4% for high-grade events [51]. Monitoring of hemorrhagic events will be an important part of further studies of SMTKIs.

Pathogenesis

The mechanisms underpinning VEGFI-induced hemorrhage are complex and not fully elucidated. VEGF has a maintenance role for normal endothelium [52]. The current hypothesis is that inhibition of VEGF decreases the renewal capacity of endothelial cells, making vessels weak and susceptible to further damage induced by trauma, inducing bleeding [53]. Inhibition of VEGF also induces nonphysiological apoptosis (rare in normostatic states) of endothelial cells, increasing susceptibility for hemorrhage [52]. Furthermore, a decrease in matrix deposition in subendothelial layers of the vasculature may also induce bleeding [54]. These physiological properties are associated with the effectiveness of VEGFIs against a variety of solid tumors,

and combination with chemotherapy gives the best effect because chemotherapy targets the tumor rim that is resistant to antiangiogenics. So, in some ways, the tumor hemorrhage can be seen as extreme effectiveness of the drugs! A combination of the above mechanisms is the most plausible cause for the hemorrhagic events associated with VEGF inhibition. However, there may be as yet unidentified effects on platelet function. The risk for hemorrhage varies among the VEGFIs, suggesting that the exact receptors and intracellular signaling pathways targeted play a role in the mechanism.

Clinical Manifestations and Management

There are two common presentations: mucocutaneous bleeding, which is often mild but more frequent, commonly manifesting as epistaxis, and serious tumor-related bleeding, which can be life-threatening and tends to occur with lung and GI tract cancers. In NSCLC patients, squamous histology is a risk factor for major pulmonary hemorrhage [50] and is now considered a contraindication to VEGFI therapy. It is unclear whether this association is a result of the histology itself or the cavitary

Table 4. Monitoring and interventions for VEGFI-induced macrovascular toxicities

Toxicity	Grading	Monitoring	Intervention
Hypertension	CTCAE version 4.0 (early trials with bevacizumab, NCI CTC version 2.0 and CTCAE version 3.0)	Monitor BP	Initiation/titration of standard BP medication (avoiding nondihydropyridine Ca ⁺⁺ channel blockers because of interference with cytochrome P450 3A4 metabolism), interruption of VEGFI if symptomatic, discontinuation of drug if grade 4 crisis occurs
Bleeding	CTCAE version 4.0	Monitor BP and platelet count	Standard resuscitation procedures, interventional techniques if appropriate, cease VEGFI for severe bleeding or cases of ICH
Perforation	CTCAE version 4.0	Patients with concerning symptoms should undergo prompt assessment including radiographic imaging with CT scan	Based on the degree of medical management required: grade I, patient is completely asymptomatic with only radiological findings; grade II, when IVT is indicated for <24 hrs; grade III, if surgical intervention, prolonged IVT, total parenteral nutrition, or tube feeding nutrition is required; grade IV, when patient develops life-threatening complications
Thromboembolism	CTCAE, version 4.0; ATE versus VTE differentiation important	None	Cease VEGFI on development of ATE and commence therapeutic anticoagulation; in cases of VTE, commence therapeutic anticoagulation, weigh risk versus benefit of continuing VEGFI

Abbreviations: ATE, arterial thromboembolism; BP, blood pressure; CT, computed tomography; CTCAE, Common Toxicity Criteria of Adverse Events; ICH, intracerebral hemorrhage; IVT, i.v. fluid therapy; NCI-CTC, National Cancer Institute Common Toxicity Criteria; VEGFI, vascular endothelial growth factor inhibitor; VTE, venous thromboembolism.

and central nature of squamous cell cancers. On this basis, cavitation, regardless of histology, is a potential risk factor for major hemorrhage and is therefore a relative contraindication [22] to VEGFI administration. A recent history of hemoptysis precludes patients from VEGFI therapy unless prior definitive and effective local therapies have been applied. VEGFIs are not safe with grade 3–4 esophageal varices in HCC patients [55]. Intracerebral hemorrhage (ICH) is a particular concern with VEGFI toxicity because of the high likelihood of fatality; however, evidence is lacking in the metastatic setting because patients with brain metastases have largely been excluded from phase II and phase III clinical trials. Small studies have reported a low likelihood of central nervous system (CNS) hemorrhage [56]; however, major CNS bleeding has been reported in a handful of patients treated with either sorafenib, bevacizumab, or sunitinib [50], and it is prudent to offer VEGFI therapy to patients

with stable brain metastases and after local measures (radiotherapy with or without surgery) have been undertaken. Higher mortality from ICH was reported in patients on sunitinib or sorafenib, but this may have been related to the effects of uncontrolled hypertension rather than hemorrhage per se [57]. The increasing use of VEGFIs in primary CNS tumors such as glioblastoma multiforme has further highlighted the concern for tumor-related hemorrhage. Data are encouraging that the risk for symptomatic ICH is low [58]. Patients with brain metastases and high-grade gliomas need to be included in future clinical trials [59].

Other definitive risk factors for hemorrhage are lacking. There is no evidence to guide the management of patients with coagulopathies or congenital/hereditary bleeding disorders treated with VEGFIs, and caution and close monitoring should apply. Macular degeneration may predispose to vitreous hemorrhage in patients re-

Figure 2. VEGFIs are targeted at tumor VEGF and VEGFR signaling. VEGF and VEGFRs are also present on vasculature throughout the body, translating to both on-target (tumor) and off-target (other vasculature) effects from VEGFIs.

Abbreviations: VEGF, vascular endothelial growth factor; VEGFI, VEGF inhibitor; VEGFR, VEGF receptor.

ceiving VEGFI therapy [60]. Interestingly, thrombocytopenia resulting from myelosuppression has not been identified as a consistent risk factor associated with bleeding events [61]. There remains a dilemma regarding the use of anticoagulants and antiplatelet agents in patients receiving VEGFIs, especially in the setting of thromboembolic events. Case reports suggest a higher risk for bleeding with therapeutic low-molecular-weight heparin and bevacizumab [62]. However, in one small study, patients on full-dose warfarin receiving bevacizumab and chemotherapy did not have a higher incidence of hemorrhagic events than patients receiving warfarin and chemotherapy alone [63]. Full anticoagulation is a frequent exclusion criterion in clinical trials so data are limited. Multivariate analysis of a large cohort study of patients with mCRC treated with bevacizumab and chemotherapy suggested that full-dose anticoagulation or antiplatelet therapy were risk factors for grade 3–4 hemorrhage, whereas prophylactic anticoagulation was not [64]. A pooled analysis of patients treated with low-dose

aspirin while receiving bevacizumab did not show a higher incidence of bleeding, but numbers were small [65] and the theoretical concern remains. More research is clearly required. Until then, caution and close monitoring are needed in patients receiving VEGFIs and anticoagulants or antiplatelets.

Recent or planned surgery is common in patients receiving or being considered for VEGFI therapy, particularly for those with CRC. Evidence to guide recommendations is again sparse, but given the theoretical concern, a 5- to 6-week “VEGFI-free” zone is advised pre- and postoperatively [66]. Theoretically, this could be reduced for SMTKIs because they have a shorter half-life. A concern that bevacizumab use in downstaging CRC liver metastases preoperatively may lead to bleeding complications is widely held, but not substantiated; therefore, a decision based on benefit versus risk must be carefully considered. Furthermore, emergency surgery is often performed in patients with advanced CRC because of obstruction from the primary

tumor, and bleeding is not necessarily a clinically significant problem perioperatively. Other complications associated with surgery and VEGFI use include wound-healing complications and GI perforation [67]. With increasing use of VEGFIs as neoadjuvant or adjuvant treatment in CRC, HCC, and RCC patients, clinical trials investigating vascular toxicities are vital. Whether a specific antidote exists or can be developed for management of major uncontrolled hemorrhage in the setting of VEGFI therapy is unknown.

Bleeding is now graded according to the NCI-CTCAE, version 4.0 (Table 2). This scale was not developed specifically with VEGFIs in mind, and its relevance and utility for describing and managing bleeding in this situation are questionable. Currently, the treatment of patients presenting with bleeding uses basic principles of hemorrhage control and resuscitation, with interventional approaches when appropriate [22].

Thromboembolism

The vascular endothelium is involved in the regulation and maintenance of the intravascular anticoagulant state [49]. Although the production of hemorrhage and thromboembolism from the same drugs may initially seem to be inconsistent, there are similar mechanisms thought to be involved with all the vascular toxicities. Thromboembolism is induced by activation of the hemostatic system [68]. Within the microvasculature, there is an extremely tightly regulated balance of pro- and anticoagulant proteins, platelet activating and inhibiting factors, and pro- and antifibrinolytic products [68]. Disruption of this intricate balance may tip the hemostatic status in either direction, promoting thromboembolism or hemorrhage. Following VEGFI therapy, endothelial cells are more susceptible to damage and apoptosis, favoring the procoagulant state and increasing the chance for both arterial thromboembolism (ATE) and venous thromboembolism (VTE) [49].

Pathogenesis

The impairment of endothelial regeneration induced by VEGF inhibition allows platelets and coagulation factors, in particular tissue factor and von Willebrand factor, to be exposed to the subendothelial procoagulant phospholipids in the basement membrane, resulting in activation the hemostatic system [53]. Other downstream effects of VEGF include involvement in the production of prostacyclin and NO by endothelial cells, both of which have antiplatelet actions and result in the promotion of thrombosis when inhibited [69]. Inhibition of VEGF may also increase hematocrit and blood viscosity,

also promoting a prothrombotic state [70]. A recent animal study posed a new hypothesis for bevacizumab-induced thrombosis [70]. It was shown that bevacizumab can induce platelet aggregation, degranulation, and thrombosis through complex formation with VEGF and activation of the platelet Fc γ RIIa receptor. However, this needs to be further explored in human samples. The greater release of procoagulant factors from the tumor itself is also able to increase the production of proinflammatory cytokines involved in several chemotherapy-induced toxicities [2, 68]. This suggests that the combination of a VEGFI and chemotherapy has the potential for additive or synergistic toxicities as well as antitumor effects [52]. VEGF may also be involved in providing survival signals for the underlying endothelium of vessels within atherosclerotic plaques [71]. This endothelium regresses without the presence of growth factors within the local microenvironment [71], which is likely to lead to instability of plaques, thus resulting in thromboembolism.

Clinical Manifestations and Management

ATEs are of greater clinical concern than VTEs in the setting of VEGFI therapy, with a meta-analysis of 1,745 patients with mCRC, NSCLC, or breast cancer demonstrating a twofold higher ATE incidence in patients receiving bevacizumab and chemotherapy than in those receiving chemotherapy alone (3.8% versus 1.7%; $p = .031$) [72]. The follow-up duration in the control arm of that meta-analysis was substantially shorter than in the bevacizumab arm, however (419 person-years versus 673 person-years), somewhat confounding the results. Subgroup analysis demonstrated that age ≥ 65 years and a prior history of an ATE were statistically significant risk factors for the development of an ATE on bevacizumab [72]. It is also likely that atherosclerotic lesions (increasing with age) may be a risk factor for an ATE. This is supported by a study by Dunmore et al. [71], in which VEGF was shown to be expressed within carotid atherosclerotic plaques, localized both adjacent and distant to vessels.

Whether or not the duration of VEGFI therapy increases the risk for an ATE is unclear, with results from an observational cohort study reporting no significant difference in ATE incidence in patients treated with <12 months of bevacizumab and those treated with ≥ 12 months of bevacizumab (2.1% versus 0.7%) [73]. This supports the theory that the vascular toxicities of VEGFI are type B adverse drug reactions (idiosyncratic, dose independent, and unpredictable). Whether pharmacogenomic variations account for the higher risk also remains uncertain. Of practical difficulty in the clinic, however, is how to use VEGFIs to treat

Table 5. Pretreatment clinic assessment of VEGFI-induced vascular toxicities compared with normal “prechemotherapy” visit

Assessment	Standard chemotherapy visit	VEGFI therapy
History	<ul style="list-style-type: none"> • Open question regarding side effects • Directed questions regarding expected toxicities: <ul style="list-style-type: none"> ○ Infection ○ Emesis ○ Mucositis ○ Appetite ○ Fatigue ○ Neuropathy 	<ul style="list-style-type: none"> • As for standard visit plus: <ul style="list-style-type: none"> ○ Headache/dizziness/visual changes (may indicate uncontrolled hypertension) ○ Abdominal symptoms (constipation, pain, fever, nausea, and vomiting) ○ Epistaxis, heavy periods, other sites of bleeding ○ Dyspnea, chest pain ○ Calf swelling and/or tenderness ○ Skin changes ○ Electronic PRO for range of symptoms
Examination	<ul style="list-style-type: none"> • Weight • Vital signs (temperature, BP, pulse) • General examination: <ul style="list-style-type: none"> ○ Respiratory ○ Cardiovascular ○ Tumor sites • Specific examination (led by history above) 	<ul style="list-style-type: none"> • As for standard visit plus: <ul style="list-style-type: none"> ○ Fundoscopy ○ Peripheral pulses ○ Capillary refill ○ Calf tenderness/swelling ○ Skin ○ Hair
Investigations	<ul style="list-style-type: none"> • Full blood examination • Renal and liver function • Magnesium • Tumor markers 	<ul style="list-style-type: none"> • As for standard plus: <ul style="list-style-type: none"> ○ Urine dipstick (protein) • And if clinically indicated: <ul style="list-style-type: none"> ○ Factor Xa (in some patients on low-molecular-weight heparin) ○ Chest x-ray, leg Doppler ultrasound, CT pulmonary angiogram, or lung ventilation perfusion scan ○ Abdominal CT ○ Brain CT

Abbreviations: BP, blood pressure; CT, computed tomography; PRO, patient reported outcome; VEGF, vascular endothelial growth factor; VEGFI, vascular endothelial growth factor inhibitor.

patients with pre-existing cardiovascular disease and a malignancy that may respond to antiangiogenic treatment. The risk–benefit ratio in these patients is unclear, because they have traditionally been excluded from clinical trials [46]. The efficacy of antiplatelet agents or low-dose anticoagulants in preventing VEGFI-related ATEs needs further investigation, although aspirin may be protective with bevacizumab [72]. It is also potentially dangerous, given the risk for hemorrhage.

Once an ATE develops in a patient receiving VEGFI therapy, it is generally recommended that the agent be permanently ceased and the ATE treated as per normal medical guidelines [22, 46, 48, 74]. However, this recommendation is from bevacizumab-derived datasets, based around certain tumor types. The question of how to manage patients with mild-to-moderate ATEs on SMTKIs remains unanswered. It will be of growing relevance to the increasing number of tumor types for which VEGFIs form the backbone of therapy.

Sunitinib and sorafenib are associated with lower rates of thromboembolic events than bevacizumab. However, semaxinib (SU5416) was withdrawn following an unacceptable rate of ATEs and VTEs in clinical trials [75]. Ax-

itinib is also associated with mesenteric vein thrombosis [76]. Reports of VTE risk vary widely, but a recent meta-analysis demonstrated a significant risk for VTEs in cancer patients receiving bevacizumab [77]. Whether or not it is safe to continue VEGFI use in patients who develop a VTE and are subsequently anticoagulated is unknown. It is also unknown whether particular anticoagulants are better suited to treatment of VEGFI-related thromboembolic events. Further clinical trials and collation of population-based data are required.

IMPACT OF TATs ON CLINICAL PRACTICE

The advent of TATs has changed oncology practice considerably. More malignancies are potentially treatable, leading to a significant increase in workload for clinicians. The side-effect profiles of anticancer regimens have expanded, and there is a need to be more aware of potential toxicities, the common and the rare, minor and major, as well as interactions between drugs. Interestingly, the FDA submission for bevacizumab reported only grade 3–5 toxicities, thereby missing the more common, lower-grade toxicities that can have such a big impact on quality of life.

Combinations of mAbs and SMTKI VEGFIs have

now been reported, looking for synergy of effect, but when synergy of toxicity has also been seen, investigators have been surprised [26]. Likewise, the combination of a VEGFI and abdominal radiotherapy is being investigated and could well lead to significant toxicity, because VEGFIs are thought to produce a radiation recall-like reaction [78]. This reinforces the need for toxicity specialists to be involved early in new drug development, because some of the adverse effects of these combinations should be predicted.

The increased use of oral agents further complicates the issues, because patients are receiving more therapy away from treatment centers. All this leads to a need to reconsider the “ideal treatment visit” for the cancer patient (Table 5). The frequency of visits needs to be rational, collection of toxicity data needs to be adequate, and the examination protocol needs to include all the common toxicities (and important rare toxicities) of the newer agents. The standard grading systems for adverse events need to be updated to include the new toxicities as well as reconsidering the grading of the old toxicities. Work by the Multinational Association for Supportive Care in Cancer on the new skin toxicity scale is a good example of how this can be done [79]. Work on capturing symptom data using wireless computer technology and patient-reported outcomes, with real-time review by cli-

nicians to tailor treatment, is progressing and is likely to be extremely useful in this setting [80].

CONCLUSIONS

Vascular complications of VEGFIs are relatively uncommon but highly important, and cannot be ignored in the clinic. As more people are treated with these agents, the burden of toxicity will continue to increase and the quality of life of these patients with longer survival times needs to be paramount. Better recording of toxicities, understanding of mechanisms, and development of ways to mitigate toxicity without reducing tumor effect are urgently needed, particularly with the potentially huge number of patients soon to be treated adjuvantly following approval of these drugs in the early cancer setting.

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