ANTIANGIOGENIC CLINICAL STRATEGIES

Adverse effects of anticancer agents that target the VEGF pathway

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Abstract | Antiangiogenesis agents that target the VEGF/VEGF receptor pathway have become an important part of standard therapy in multiple cancer indications. With expanded clinical experience with this class of agents has come the increasing recognition of the diverse adverse effects related to disturbance of VEGF-dependent physiological functions and homeostasis in the cardiovascular and renal systems, as well as wound healing and tissue repair. Although most adverse effects of VEGF inhibitors are modest and manageable, some are associated with serious and life-threatening consequences, particularly in high-risk patients and in certain clinical settings. This Review examines the toxicity profiles of anti-VEGF antibodies and small-molecule inhibitors. The potential mechanisms of the adverse effects, risk factors, and the implications for selection of patients and management are discussed.

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Introduction

To date, three agents that primarily target the VEGF/VEGF receptor (VEGFR) pathway have been approved by the FDA for cancer therapy: a humanized monoclonal antibody (mAb), bevacizumab, and two small-molecule receptor tyrosine kinase inhibitors (TKIs), sorafenib and sunitinib. Furthermore, a large number of investigational anti-angiogenesis agents are in the late stage of clinical development. As the VEGF pathway is not only essential for normal growth and development, but also critical to physiological response and homeostasis in many organs and functions in adulthood,[1] a variety of adverse effects were anticipated with pharmacological blockage of this pathway. Indeed, the clinical adverse event profiles are extensive. The adverse effects attributed to VEGF inhibition include hypertension, arterial thromboembolic events (ATEs), proteinuria or renal dysfunction, wound complications, hemorrhage, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome (RPLS; Box 1).

The molecular mechanisms of the adverse effects of VEGF/VEGFR inhibitors are not fully understood. VEGF is expressed in almost all organ tissues and upregulated in response to stress or injury. Interaction of VEGF with VEGFR on endothelial cells (ECs) induces production of nitric oxide and prostaglandin I_2, both of which are important for EC survival, proliferation and migration, as well as vasodilatation and prevention of blood cell adherence to the EC lining (Figure 1). Inhibition of the VEGF pathway might, therefore, impair angiogenesis, disrupt vascular integrity, and disturb the normal EC interaction with platelets and surrounding tissues (Figure 1). Proposed mechanisms for some of the adverse events associated with these agents are summarized in Box 2.

Competing interests
The authors declare no competing interests.

Both mAbs and TKIs that target VEGF and VEGFR share the class adverse effects as a result of VEGF/VEGFR inhibition. The mAbs and TKIs are, however, distinctive in their pharmacological features, such as their direct targets, specificities and pharmacokinetics (Table 1). Therefore, the extent of 'on target' anti-VEGF effects may differ with these agents. In addition, VEGFR TKIs are also associated with variable additional toxic effects due to their non-specific effect on other receptor tyrosine kinases (Box 1). Although most adverse events of VEGF/VEGFR inhibitors are manageable, a number of rare events are serious, and can have rapid, life-threatening consequences. The spectrum of adverse events in individual patients and different disease settings is variable, and may reflect the combined effect of several factors: dose and specificity of the anti-VEGF drug; tumor histology; extent and locations of the tumors; local or systemic comorbid conditions in the host; and the concurrent anticancer agents in the treatment regimen (Table 2).

This Review will examine the adverse events associated with VEGF- and VEGFR-targeted therapies when used as monotherapy or when used in combination regimens, with a focus on the FDA-approved agents bevacizumab, sorafenib and sunitinib. Potential mechanisms of actions and implications for the management of patients will be discussed.

Cardiovascular adverse effects

Hypertension

Hypertension is the best documented cardiovascular adverse effect of VEGF/VEGFR inhibitors.[2,3] VEGFR2 signaling generates nitric oxide and prostaglandin I_2, which induces EC-dependent vasodilatation in arterioles and venules,[4,5] the component of vasculature that has most impact on blood pressure. Blockage of VEGF would

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Key points

- Adverse effects associated with both VEGF- and VEGFR-targeting monoclonal antibodies and tyrosine kinase inhibitors are diverse, and include hypertension, arterial thromboembolic events, proteinuria, bowel perforation, reversible posterior leukoencephalopathy syndrome, wound complications and hemorrhage
- Risk of serious adverse events may be increased by a multitude of risk factors related to the tumor characteristics and locations, comorbidities, and prior or concurrent anticancer therapy
- Risk–benefit assessment is important for individual patients considering antiangiogenesis therapy
- In order to provide evidence-based guidance for risk identification, toxicity management and treatment adjustment for antiangiogenesis agents further research in this area is warranted

Box 1 | Adverse effects of agents that target the VEGF pathway

'Class' adverse effects related to VEGF blockage
- Hypertension
- Proteinuria
- Arterial thromboembolic events (that is, cardiac ischemia, cerebral vascular accident, peripheral arterial thrombosis)
- Cardiomyopathy
- Hemorrhage (submucosal or tumor-related)
- Wound complications (delay or impaired wound healing)
- Gastrointestinal perforation, fistula formation
- Reversible posterior leukoenkephalopathy syndrome

Adverse effects with unclear correlation to VEGF blockage
- Hypothyroidism (sunitinib, cediranib)
- Myelosuppression (sunitinib, sorafenib)

Other adverse effects of TKIs not related to VEGF blockage
- Hand-foot syndrome (sorafenib)
- Mucositis
- Skin reactions
- Hypophosphatemia
- Increased lipase

lead to vasoconstriction. Rarefaction (decreased arteriole and capillary densities), which is observed in noncancer patients with hypertension,[6] has also been hypothesized as a mechanism of hypertension induced by anti-VEGF therapy;[7] however, at this time, whether antiangiogenesis agents directly cause rarefaction is not clear.

The effect of anti-VEGF agents on blood pressure is dose-dependent and the extent of hypertension might reflect the extent of target inhibition. In a phase II study in patients with renal-cell carcinoma (RCC) treated with either placebo, 3 mg/kg bevacizumab or 10 mg/kg bevacizumab, the rate of hypertension was significantly higher in the high-dose group (36%) compared with the low-dose group (3%).[8] With small-molecule VEGFR TKIs, the increment rise in blood pressure was also proportional to dose;[9] however, dose escalation of a given TKI may be limited by non-VEGFR-related toxic effects, depending on the relative potency of the agent against various targets. For example, while hand-foot syndrome and fatigue were dose-limiting for sorafenib and sunitinib, and defined the maximum tolerated dose (MTD),[10–12] more-specific and potent VEGFR TKIs, such as cediranib and axitinib, are associated with a higher rate of hypertension compared to sunitinib or sorafenib at the MTD.[13] Pharmacokinetic data demonstrates that cediranib[14] and axitinib[15,16] inhibit VEGFR2 at lower concentrations (half maximal inhibitory concentration [IC_{50}] <1 nM) compared to their inhibitory effects on other targets such as platelet-derived growth factor receptor (PDGFR). In the case of sorafenib, the relative potency against VEGFR2 (IC_{50} = 90 nM) is weaker compared with potency against other targets.[17]

In addition to dose and inherent differences between agents, host susceptibility can also affect the rate of hypertension. Patients with pre-existing hypertension are generally more likely to develop further elevation in blood pressure when receiving anti-VEGF therapy. The risk of hypertension related to anti-VEGF therapy is also higher in patients with metastatic RCC compared to other indications. In a phase III trial of sorafenib versus placebo in patients with RCC, hypertension was reported in 17% of patients treated with sorafenib,[18] while in a phase III trial in patients with hepatocellular carcinoma (HCC), the rate of hypertension associated with the same dose of sorafenib was only 5% (Table 3).[19] A similar trend was also observed in phase III trials of sunitinib in patients with RCC and gastrointestinal stromal tumors (GIST).[20,21] In a retrospective study in patients with breast cancer treated with bevacizumab alone or combined with paclitaxel, genetic susceptibility to hypertension was explored based on single nucleotide polymorphisms of selected VEGF and VEGFR2 loci. The study suggested that certain *VEGF* polymorphisms might be associated with a lower risk of grade 3 or 4 hypertention.[22] These findings, however, are preliminary and remain to be validated in more patients in independent datasets.

The frequencies and grades of hypertension associated with bevacizumab, sorafenib and sunitinib treatment based on results from randomized trials are shown in Tables 3 and 4. The hypertension rates reported for several investigational VEGFR TKIs used at the recommended phase II doses in patients with RCC are also included. Grading of hypertension is based on the National Cancer Institute Common Toxicity Criteria of Adverse Events (CTCAE). According to the latest version of this criteria (CTCAE v3.0) implemented in 2003, grade 3 hypertension is defined as 'requiring more than one drug or more-intensive therapy than previously'. Early clinical trials, including a few pivotal trials of bevacizumab, were based on the previous CTCAE version (v2.0), in which hypertension requiring only one blood pressure medication would be defined as grade 3 (the same degree of hypertension would be considered grade 2 in the current CTCAE v3.0 criteria). This difference in grading may explain in part the apparently lower incidence of grade 3 hypertension in more-recent trials with the same agent in the same indication; for example, E2100 compared to AVADO (Table 3).

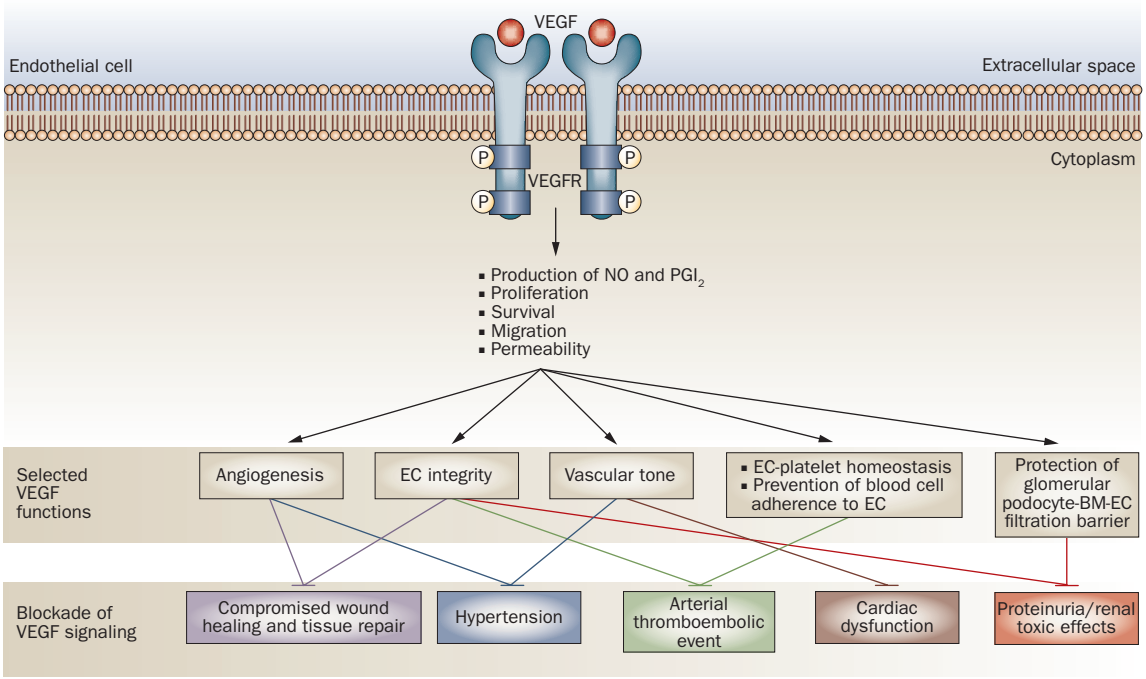

Figure 1 | Selected physiological functions of VEGF/VEGFR signaling and consequence of the pathway blockage. VEGF signaling via VEGFR on ECs leads to downstream molecular and cellular events including production of NO and PGI_2, increase in permeability and EC proliferation, survival, and migration. These VEGF-dependent effects are essential for physiological functions and processes such as angiogenesis and homeostasis of the EC–platelet interactions and vascular tone (vasodilation); maintenance of the integrity and antithrombotic/antiadherent state of the EC lining; and protection of the glomerular filtration barrier. Blockage of VEGF signaling can disrupt the vascular homeostasis and physiological response to stress, with diverse pathological consequences that include compromised wound healing and tissue repair, hypertension, arterial thromoembolic events, cardiac dysfunction, and renal toxic effects. Abbreviations: BM, basement membrane; EC, endothelial cells; P, phosphorylated residues; PGI_2, prostaglandin I_2; NO, nitric oxide.

Management of hypertension

In order to prevent life-threatening complications, while minimizing delay and/or dose attenuation of anticancer therapy, close monitoring of blood pressure and timely initiation or titration of hypertension medications are critical. In patients with cancer, the primary goal of hypertension management is to maintain an acceptable blood pressure level to allow safe delivery of antiangiogenesis therapy. Further optimization of hypertensive medication, however, should be considered to achieve better blood pressure controls to the level consistent with goals in general medical practice. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) stipulate that target blood pressure control should be <140/90 mmHg in the general population, and <120/80 mmHg in patients with diabetes or renal dysfunction.[23] Although this ideal blood pressure target does not need be reached to allow continuation of antiangiogenesis therapies, given the effectiveness of hypertensive medication, this goal should be achievable in most patients.

A variety of hypertensive medications, including diuretics, beta-blockers, angiotensin-converting-enzyme inhibitors and calcium-channel blockers, have all been used to treat hypertension induced by anti-VEGF and anti-VEGFR agents. Each of these agents has been effective on an individual patient basis, and no data are currently available to suggest one agent is better than another. A few factors, however, may affect the selection of specific agents, for example, presence of ventricular dysfunction or tachycardia, or likelihood of pharmacokinetic interactions with specific VEGFR TKIs.

Hypertension can be controlled with standard oral hypertensive medications in most cases where therapeutic doses of these anti-VEGF agents are used. In rare cases, however, a patient may develop uncontrolled hypertension or hypertensive crisis (grade 4), with life-threatening complications. Interruption of anti-VEGF therapy would be necessary if a patient is symptomatic or if the level of blood pressure elevation is a concern for the development of acute complications. Treatment with anti-VEGF therapies can be resumed at the same or reduced dose when blood pressure control is achieved with appropriate hypertensive medications. In patients who develop hypertensive crisis, permanent discontinuation of anti-VEGF therapy is recommended, as the safety of resuming therapy in such patients is unknown.[24]

Arterial thromboembolic events

The underlying pathogenesis of venous and arterial thrombosis are differentially associated with certain distinctive

Box 2 | Possible mechanisms of adverse effects related to VEGF inhibition

Hypertension
- Decrease in nitroxide and prostaglandin I_2 production leading to inhibition of vasodilatation
- Decrease in arteriole and capillary density (rarefaction)

Arterial thrombosis
- Endothelial cell apoptosis
- Disturbance of platelet–endothelial cell homeostasis; platelet aggregation
- Exposure of extracellular matrix to blood cells

Cardiomyopathy
- Increase in peripheral vascular resistance
- Inhibition of VEGF-dependent cardiomyocyte growth in response to ischemia or blood pressure elevation
- Ischemic changes in coronary arterioles

Proteinuria and renal adverse effects
- Disturbance of VEGF-dependent function and interaction between endothelial cells and podocytes in the filtration barrier of glomeruli
- Thrombotic microangioapathy
- Endothelial cell damage

Wound healing issues
- Impaired neovascularization
- Disturbance of platelet–endothelial cell interaction
- Reduction in the VEGF-induced tissue factor on endothelial cell results in compromised coagulation cascade and platelet activation

Bowel perforation
- Ischemic changes in intestinal walls
- Impaired wound healing

Table 1 | Differences between adverse effects caused by anti-VEGF mAbs and TKIs

Drug characteristics	Drug class	
	mAbs	TKIs
Main targets	VEGFA (bevacizumab)	VEGFR2, VEGFR3, Raf, PDGFR, KIT, and RET (sorafenib) VEGFR1–3, PDGFR, KIT, FLT-3 (sunitinib)
Mechanisms of action on VEGF pathway	Extracellular: blocks ligand-receptor binding	Intracellular: inhibits signaling of the VEGFR receptor tyrosine kinase
Adverse effects	Class adverse effects related to inhibition of VEGF pathway	Class adverse effects related to inhibition of VEGF pathway Other adverse effects related to inhibition of additional targets
Drug half-life	Long (20 days)	Short (<24 h)

Abbreviations: FLT-3, FMS-like tyrosine kinase 3; mAbs, monoclonal antibodies; PDGFR, platelet-derived growth factor receptor; TKIs, tyrosine kinase inhibitors.

features, although some mechanisms are partially overlapping. For example, while the coagulation cascade, mainly regulated by tissue factor, is involved in venous thrombosis, arterial thrombosis is mediated primarily by platelets.[25] The importance of VEGF in EC–platelet homeostasis may explain the propensity of VEGF inhibitors to increase the risk of ATEs. Under normal physiological conditions, secretory factors, such as VEGF from ECs and platelets, have a major role in preventing adherence of blood cells to the vasculature, as well as maintaining EC survival and renewal in response to vascular injury. When VEGF signaling is blocked by bevacizumab or VEGFR TKIs, this may compromise the integrity of the EC lining and promote platelet aggregation.

The clinical evidence for an increased risk of ATEs with VEGF inhibitors was first identified in a pooled analysis of five randomized trials encompassing 1,745 patients randomly allocated to chemotherapy alone or chemotherapy plus bevacizumab for the treatment of metastatic colorectal cancer (CRC), breast cancer and non-small-cell lung cancer (NSCLC; Table 5).[26] Compared with chemotherapy alone, the addition of bevacizumab to chemotherapy was associated with a twofold increase in ATEs (3.8% versus 1.7%; $P=0.031$). A similar increase in ATEs was also observed in randomized studies with sorafenib (Table 5). Although cardiac and cerebral ischemia are the most common manifestations, ATEs during anti-VEGF therapy have rarely presented as aortic or peripheral artery thromboses.[27]

The increase of ATEs by anti-VEGF therapy was further exacerbated in elderly patients or those with a history of ATEs. In the subgroup of patients with both risk factors in the above mentioned pooled analysis of bevacizumab trials, as many as 17.9% of patients developed an ATE.[26] Given the lack of early warning signs in most ATEs, careful risk–benefit assessment before initiating antiangiogenesis therapy is essential. VEGF/VEGFR inhibitors should be immediately discontinued in patients who develop an ATE. Although aspirin is commonly used in ATEs as standard care, whether aspirin is effective in reducing the risk of ATEs related to anti-VEGF therapy is not known.

Ventricular dysfunction and CHF

The potential risk of cardiomyopathy with VEGF/VEGFR inhibitors is suggested in cardiomyocyte-specific VEGF knockout mouse models, which present with dilated cardiomyopathy.[28] In the developed heart, VEGF is important for maintaining cardiomyocyte well-being in response to stress and injury. Additional molecular pathways targeted by TKIs may also play a role. For example, PDGFR, a target of sunitinib and sorafenib, is expressed on cardiac myocytes[29] and is a potent stimulus of normal cardiomyocyte growth under hypertensive stress.[30]

Cardiomyopathy and congestive heart failure (CHF) have been reported with the use of VEGF- and VEGFR-targeting agents, including bevacizumab and sunitinib.[24,31] However, few trials have included prospective cardiac monitoring, and therefore, the extent of asymptomatic ventricular dysfunction cannot be fully assessed. Results from randomized trials with bevacizumab indicate an increase in clinically significant CHF in patients with prior exposure to anthracycline.[24,32] In patients with metastatic breast cancer refractory to anthracycline and taxane therapy, symptomatic cardiomyopathy was reported in

Table 2 | Factors that may increase the risk of adverse events with anti-VEGF therapy

Adverse effect	Cancer-related risk factors	Host-related risk factors	Treatment-related risk factors (concurrent or prior anticancer therapy)
Hypertension	Renal-cell carcinoma	Pre-existing hypertension	Unknown
Arterial thromboembolic event	Unknown	Elderly History of arterial thromboembolic events	Unknown
Cardiomyopathy (CHF)	Unknown	History of cardiac disease (e.g. coronary artery disease, hypertension)	Anthracycline
Gastrointestinal perforation	Colorectal cancer Ovarian cancer Gastric cancer	Diverticulitis, ulcer, infection, obstruction Prior surgery Ischemic bowel	Radiotherapy Surgery
Fistula	Primary lung cancer (brohco-esophageal fistula) Head and neck cancer	Unknown	Radiotherapy
Hemorrhage	NSCLC (especially with squamous histology or cavitation) Gastrointestinal cancers	Unknown	Radiotherapy
Myelosuppresion and infection	Unknown	Poor performance status at baseline Elderly	Chemotherapy regimens

Abbreviations: CHF, congestive heart failure; NSCLC, non-small-cell lung cancer.

Table 3 | Hypertension associated with bevacizumab therapy

Tumor type and drug trial name	*n*	Treatment regimens	Hypertension grade	Patients with hypertension (%)		
				Control	Bevacizumab (5 mg once every 2 weeks or 7.5 mg once every 3 weeks)	Bevacizumab (10 mg once every 2 weeks or 15 mg once every 3 weeks)
RCC[8] (T98-0035)	116	Placebo vs bevacizumab	All grade Grade 3–4[a]	5.01 0	2.7[c] 0[c]	35.9 20.5
RCC[49] (B017705E)	649	IFN-α vs bevacizumab + IFN-α	All grade Grade 3–4[b]	9.0 <1.0	NA	26.0 3.0
CRC[45] (AVF2107g)	813	Chemotherapy vs bevacizumab + chemotherapy	All grade Grade 3[a]	8.3 2.3	22.4 11	NA
CRC[93] (N016966)	1,369	Chemotherapy vs bevacizumab + chemotherapy	Grade 3–4[b]	1.0	4.0	NA
Breast cancer[32] (AVF2119g)	463	Chemotherapy vs bevacizumab + chemotherapy	All grade Grade 3–4[a]	2.3 0.5	NA	23.6 17.9
Breast cancer[46] (E2100)	722	Chemotherapy vs bevacizumab + chemotherapy	Grade 3–4[a]	0	NA	14.8
Breast cancer[94] (AVADO)	736	Chemotherapy vs bevacizumab + chemotherapy	Grade 3–4[b]	1.3	0.4	3.2
NSCLC[48] (E4599)	878	Chemotherapy vs bevacizumab + chemotherapy	Grade 3[a] Grade 4	0.5 0.2	NA	6.8 0.2
NSCLC[95] (B017704)	1,043	Chemotherapy vs bevacizumab + chemotherapy	Grade 3–4[b]	<1.0	1.5	<1.0

[a]Definition of grade 3 hypertension based on CTCAEv2.0: Requires initiation or increase medication. [b]Definition of grade 3 hypertension based on CTCAEv3.0: Requires more than one drug or more intensive therapy than previously. [c]Patients treated at 3 mg/kg every two weeks. Abbreviations: CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; IFN-α, interferon alpha; NA, not applicable; NSCLC, non-small-cell lung cancer; RCC, renal-cell carcinoma.

3% of patients (7 of 229) treated with bevacizumab plus chemotherapy compared with 1% (2 of 215) in the chemotherapy control arm.[32] Results from a phase III trial of bevacizumab with or without paclitaxel as first-line treatment for metastatic breast cancer showed similar CHF rates of 2.2% versus 0.3%; importantly, in the subset of patients exposed to anthracycline in the adjuvant setting, the CHF rates were 3.6% versus 0.6%.[24]

The safety of concurrent use of anthracycline and anti-VEGF agents has not been fully established. Single-arm studies in metastatic disease settings indicate that bevacizumab in combination with high cumulative doses of

Table 4 | Hypertension associated with VEGFR TKIs[a]

Treatment regimen	Tumor type	*n*	Patients with hypertension (%)		
			Hypertension grade	Control	VEGFR TKI
IFN-α vs sunitinib (50 mg daily for 4 of 6 weeks)	RCC[21]	735	All grade Grade 3–4	1 1	24 8
Placebo vs sunitinib (50 mg daily for 4 of 6 weeks)	GIST[20]	312	All grade Grade 3–4	4 0	10.4 3.0
Placebo vs sorafenib (400 mg twice daily)	RCC (TARGET)[18]	903	All grade Grade 3–4	2 <1	17 4
Placebo vs sorafenib (400 mg twice daily)	HCC (SHARP)[19]	599	All grade Grade 3–4	2 1	5 2
Cediranib (45 mg daily)	RCC[96]	43	Grade 3–4	NA	30.2
Axitinib (5 mg twice daily)	RCC[50]	52	All grade Grade 3–4	NA	57.7 15.4
Pazopanib (800 mg daily)	RCC[97]	225	All grade Grade 3–4	NA	40.0 8.0

[a]All studies except the one that assessed pazopanib, defined grade 3 hypertension based on CTCAEv3.0. Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; IFN-α, interferon alpha; NA, not applicable; RCC, renal-cell carcinoma; TKI, tyrosine kinase inhibitor.

anthracycline may be associated with an excessive rate of heart failure.[33,34] In adjuvant studies in patients with breast cancer who received bevacizumab and a limited cumulative dose of doxorubicin (<300 mg/m^2), preliminary safety results supported the feasibility of testing the combination in large-scale adjuvant trials.[35] Longer follow-up and additional data from ongoing randomized trials are needed to fully define the impact of bevacizumab on cardiac function when combined concurrently with doxorubicin in the adjuvant setting.

Cardiomyopathy has been associated with sunitinib monotherapy. In an early phase I–II trial with this agent, which incorporated careful cardiac monitoring,[36] 75 patients with imatinib-refractory GIST were treated for a median of 33.6 weeks (range, 3.3–112 weeks). A drop in left ventricular ejection fraction (LVEF) below the normal range (that is, <50%) was observed in 20% of patients, and 8% developed clinical CHF.[36] Cardiac biopsy samples obtained from patients with sunitinib-induced CHF[36,37] demonstrated cardiomyocyte hypertrophy and swollen mitochondria with no evidence of inflammation, edema, or fibrosis. In phase III trials of sunitinib versus placebo in patients with imatinib-refractory GIST or metastatic RCC, the rate of LVEF decline was 10%, with 2–3% patients developing grade 3 CHF.[21,38] The different cardiac event rates observed between these phase II and III trials were not well explained, but might be related to variable prior exposure to cardiotoxic agents (for example, anthracyclines), pre-existing cardiac risk factors, or the duration of therapy and follow-up times.

Refractory CHF with fatal outcomes has rarely been reported in trials of antiangiogenic agents. In most patients ventricular dysfunction improved after cessation of the anti-VEGF agent. Whether recovery was due to a true reversibility of the adverse effect, efficacy of cardiac medications, or a combination of the two is not clear. At this time the safety of resuming anti-VEGF therapy after recovery of ventricular dysfunction has not been established.

Renal adverse effects

The filtration barrier of the renal glomeruli is formed by ECs, podocytes, and basement membrane components. Interaction of VEGF produced by podocytes with VEGFR2 on glomerular ECs is critical to the normal function and repair of the system. In preclinical murine models, heterozygous deletion of *VEGF* in podocytes led to loss of EC fenestration, loss of podocytes, mesangiolysis, and proteinuria.[39,40] More importantly, VEGF was also shown to have a critical protective role in the pathogenesis of microangiopathic process.[41] Clinically, renal adverse effects may present as asymptomatic proteinuria following anti-VEGF therapies, and rarely, acute renal failure, nephrotic syndrome, or microangiopathy can also develop. The underlying pathological changes are not always clear. In the few cases where renal biopsies were performed, pathological findings have included proliferative glomerulonephritis, interstitial nephritis,[42] and thrombotic microangiopathy.[43,44]

Proteinuria

Proteinuria has been observed in all studies of bevacizumab to date, and is usually mild and asymptomatic. Significant increase in urine protein (grade 3, >3.5 g protein per 24 h urine) is less common, occurring in 3% of patients in most clinical trials,[45–48] and in up to 7–8% of patients with RCC.[8,49] In rare cases, patients with asymptomatic proteinuria can progress to nephrotic syndrome (<0.5% of patients)[24] or renal failure that requires dialysis.

Patients treated with bevacizumab should be monitored for proteinuria, by either dipstick or calculation of the urine protein:creatinine ratio on spot urine samples. Quantification of 24 h urine protein is recommended if spot urine tests indicate significant proteinuria (for example, 2+ on dipsticks or 2.0 by urine protein:creatinine ratio). Anti-VEGF agents should be interrupted if 24 h urine protein exceeds 2.0 or 3.5 g, and these agents should be permanently discontinued upon development of nephrotic syndrome.

Interestingly, proteinuria is rarely reported in clinical trials with sunitinib or sorafenib, although how closely patients were monitored for this adverse effect is unclear. With axitinib, a potent and specific VEGFR TKI, 32% of patients (17 of 52) with RCC developed grade 2 or higher proteinuria (as measured by a dipstick), and a few patients had proteinuria >1 g per 24 h urine.[50]

Renal thrombotic microangiopathy

Thrombotic microangiopathy (TMA) has been described in biopsy samples from case reports of patients treated with bevacizumab,[41,43,44] VEGF-Trap,[51] and sunitinib.[52–54] TMA associated with VEGF/VEGFR inhibitors was mostly localized to the kidney, and systemic manifestations (for example, thrombocytopenia or schistocytosis) were

present only in some of these patients.[52] As renal biopsies were rarely performed in patients with proteinuria or renal insufficiency, the true rate of renal-localized or subclinical TMA is not assessable. Available data indicate that systemically evident TMA (that is, with evidence of hemolysis or thrombocytopenia) is very rare with anti-VEGF therapies. However, the use of more than one anti-VEGF agent in combination might enhance the risk. In a phase I dose-escalation trial of concurrent bevacizumab (10 mg/kg every 2 weeks) and escalating doses of sunitinib (25 mg, 37.5 mg or 50 mg daily for 4 out of 6 weeks) in patients with RCC, 5 of the 12 patients at the highest dose level developed systemic TMA, or microangiopathic hemolytic anemia; clinical presentations in these cases included thrombocytopenia, schistocytes, hypertension and varying degrees of protienuria.[55]

Hemorrhage

The risk of bleeding is increased in patients treated with VEGF- and VEGFR-targeting agents. Two distinctive types of bleeding have been described: mild spontaneous mucocutaneous bleeding and serious tumor-related bleeding. In all trials of bevacizumab, mucocutaneous hemorrhage has been seen in 20–40% of patients, with mild epistaxis being the most common presentation. Mucocutaneous bleeding and epistaxis have also been associated with sunitinib,[21] and other VEGF/VEGFR inhibitors such as axitinib[56] and VEGF-Trap.[57]

Among different clinical settings, tumors in the lungs and gastrointestinal tract are associated with the highest risk and greatest severity of bleeding following anti-VEGF therapies. In a phase II pilot study where 66 patients with metastatic NSCLC were treated with bevacizumab and chemotherapy, six cases of life-threatening hemoptysis were reported, four of which were fatal.[58] Subset analysis has suggested squamous histology as a risk factor, although whether it was the histology *per se,* or its association with central location and cavitation that was central to the risk is unclear. In a phase III NSCLC trial (E4599) that excluded patients with squamous histology, grade 3–5 pulmonary hemorrhage events were 2.3% (10 of 427 patients) in the bevacizumab and chemotherapy arm compared with 0.5% (2 of 441) of those treated with chemotherapy only.[24] Five of the hemoptysis events in the bevacizumab-containing arm were fatal.

Pulmonary hemorrhage with fatal outcome was also reported in patients with NSCLC treated with sorafenib,[59] sunitinib,[60] axitinib,[50] and motesanib.[61] Similar to the experience observed with bevacizumab, most of these bleeding events were in patients with squamous histology.

Advanced squamous NSCLC is contraindicated for bevacizumab therapy. Definitive risk factors in other NSCLCs have not been identified; however, a case–control analysis indicated that most hemoptysis occurred in patients who developed tumor cavitation before or during bevacizumab therapy.[62] Although not a standard contraindication, presence of cavitation should be considered a potential risk factor in the risk–benefit assessment of antiangiogenesis therapy in NSCLC.

Table 5 | Arterial thromboembolism associated with VEGF/VEGFR targeting agents[d]

Disease (trial designation)	*n*	Treatment regimen	Percentage of events (%)	
			Control	VEGF/VEGFR inhibitor
Bevacizumab				
Pooled analysis (CRC, breast cancer, NSCLC)[26]	1,745	Chemotherapy vs bevacizumab + chemotherapy	1.7	3.8[a]
Breast cancer (E2100)[46]	711	Chemotherapy vs bevacizumab + chemotherapy	0[b]	1.9[b]
NSCLC[24]	878	Chemotherapy vs bevacizumab + chemotherapy	1.4	3.0
CRC (E3200)[47]	829	Chemotherapy vs bevacizumab vs bevacizumab + chemotherapy	0.4	0.6[c]
CRC (BRiTE)[98]	1,953	Chemotherapy + bevacizumab	NA	1.8
Sorafenib				
RCC[18]	903	Placebo vs sorafenib	<1[b]	3[b]
HCC[19]	599	Placebo vs sorafenib	1	3

[a]Pooled analysis of five different trials in which bevacizumab was given at doses of 5 mg once every 2 weeks, 7.5 mg once every 3 weeks, 10 mg once every 2 weeks or 15 mg once every 3 weeks. [b]Cardiac ischemia. [c]Includes all bevacizumab-containing regimens. [d]Unless specified, ATE rate refers to a combination of cardiac ischemia (angina, myocardial infarction), cerebral ischemia (transient ischemic attack, cerebrovascular accident) and peripheral arterial or bowel ischemia. Abbreviations: ATE, arterial thromboembolic event; CRC, colorectal cancer; NA, not applicable; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; RCC, renal-cell carcinoma.

Bleeding associated with gastrointestinal tumors was also increased with antiangiogenesis therapy. In the pivotal phase III trial in patients with advanced CRC, the incidence of gastrointestinal hemorrhage was 24% in the bevacizumab plus chemotherapy arm compared with only 6% in the chemotherapy control group, with 3.1% versus 2.5% being grade 3–4 in severity.[24]

In a phase III trial of sunitinib in GIST, 3% of patients treated with sunitinib developed grade 3–4 bleeding from the tumor sites, while no such events occurred in those in the placebo arm.[31] In a randomized phase II trial of sorafenib combined with dacarbazine in patients with melanoma, central nervous system (CNS) bleeding was reported in 8% of sorafenib-treated patients and no bleeding was reported in the control arm; three of the four CNS bleeding events occurred at the site of tumor progression.[63]

Fistular formation and GI perforation

A number of effects on local tissues by VEGF blockage, including hypoxia and impaired wound healing, could increase the risk of bowel perforation and fistula formation in the setting of tumor involvement or bowel inflammation. As expected, the risk of bowel perforation or gastrointestinal fistula is more prominent in patients with intra-abdominal tumors, such as colorectal, gastric, pancreatic, and ovarian cancers (Table 6). In patients with metastatic CRC treated with bevacizumab, the rate of bowel perforation or gastrointestinal fistula was around 2.4%, compared with <1% in the comparator arms.[24] The

Table 6 | Incidence of bowel perforations in clinical trials of bevacizumab treatment

Trial name and/or study phase	*n*	Treatment regimen	Incidence of bowel perforation (%)		Disease setting
			Control arm	Bevacizumab arm	
Colorectal cancer					
Pivotal[45]	813	Chemotherapy vs bevacizumab + chemotherapy	0–<1	1–1.8	Metastatic
Roche[93]	1,401				
E3200[47]	829				
NSABP-C08[70]	2,710		0.2	0.3	Adjuvant
Breast cancer					
E2100[46]	722	Chemotherapy vs bevacizumab + chemotherapy	0–<1	0.4–0.5	Metastatic
AVADO[94]	736				
Ovarian cancer					
Phase II (GOG170D)[64]	62	Bevacizumab	NA	0	Metastatic (second-line or third-line)
Phase II (ORBIT)[65]	44	Bevacizumab	NA	11.4	Metastatic (second-line or greater)
Phase II[99]	70	Bevacizumab + chemotherapy	NA	4.3	Metastatic (second-line or third-line)
Phase II[100]	23	Bevacizumab+ chemotherapy	NA	9	Metastatic (second-line or greater)

risk of bowel perforation after treatment with bevacizumab is also increased in patients with metastatic ovarian cancer, although the incidences were variable across trials, ranging from 0% (0 of 62)[64] to as high as 11.4% (5 of 44).[65,66] Patients with more-advanced-stage tumors seem to be at particularly high risk, probably related to more-extensive mesenteric tumor seeding, as well as more frequent bowel inflammation or obstruction. Although tumor involvement is a common finding around the gastrointestinal perforation, other underlying conditions have included diverticulitis, gastric ulcer, surgical wound (including anatomosis), and bowel ischemia.

Gastrointestinal perforation and fistula have also been reported during treatment with sunitinib and sorafenib.[31,67] However, as clinical trials with these two agents are largely limited to RCC, HCC and GIST, the risk compared with controls has not been adequately established. Bowel perforation may present with nonspecific symptoms, such as abdominal pain, nausea, and fever. In some cases, the manifestations could be abdominal or perirectal abscess without overt signs of free air on X-rays. As prompt intervention is critical to favorable outcomes, gastrointestinal perforation should be considered in the differential diagnosis in patients who develop abdominal symptoms while on antiangiogenesis therapy.

Currently, safety of resuming anti-VEGF agents after recovery from treatment-emergent bowel perforation is unknown, as most clinical trials mandate discontinuation of the protocol therapy upon development of bowel perforation. In addition, no evidence-based guidance exists for the optimum interval between prior history of bowel perforation and initiation of anti-VEGF therapies. In general, for patients being considered for antiangiogenic therapy, it would be important to ensure resolution or adequate control of the underlying risk conditions, as well as complete recovery and healing from the prior bowel perforation.

Wound complications

Wound healing is a complex process involving angiogenesis and closely regulated interactions between ECs, platelets, and the coagulation cascade. Inhibition of the VEGF pathway has a diverse effect on local tissues that could disrupt the normal healing process. Antiangiogenic agents are known to delay cutaneous wound healing in a dose-dependent manner in animal models.[68]

In clinical use of anti-VEGF or anti-VEGFR agents, impaired wound healing at the surgical site may have two implications: firstly, dehiscence of a previously healed wound in patients who had surgery before initiating the anti-VEGF therapy, and secondly, delay or failure of wound healing in patients who underwent surgery following treatment with an anti-VEGF or anti-VEGFR agent. Most clinical trials with antiangiogenesis therapies require at least 28 days from any major surgery before starting treatment. In a retrospective analysis of randomized trials in metastatic CRC, for a subset of patients who had surgeries 28–60 days before initiating bevacizumab, the incidence of wound complications were low (1.3%),[69] indicating that the 28-day interval from colonic surgery (colectomy) might be appropriate. The phase III adjuvant trial (NSABP-C08) in patients with CRC who received bevacizumab and chemotherapy at least 28 days (median 46) after colectomy confirmed that the rate of serious wound complications (grade 3 or higher) was low (1.7%; 23 of 1,326); however, this rate was significantly higher than that in the chemotherapy-alone control arm (0.3%; 4 of 1,321) (P<0.01).[70] Whether the same interval is appropriate for surgeries of different location or extent is not known. Ongoing adjuvant or postoperative treatment

trials in patients with breast cancer, NSCLC and glioma will provide the opportunity to assess more systemically the risk and optimal timing of antiangiogenesis therapy following surgery.[71]

The optimal interval from interruption of antiangiogenesis therapy to surgery has not been determined, but might depend on the nature of the surgery and, perhaps more importantly, the half-life of the agents. Bevacizumab has an average half-life of 20 days (range 11–50 days),[72] and residual drug exposure can persist for weeks to months. In a retrospective subset analysis of data from patients with metastatic CRC undergoing emergent surgery while on study, 13% of patients (10 of 75) in the bevacizumab arm developed grade 3 to 4 postoperative wound complications compared to 3.4% of patients (1 of 29) in the chemotherapy arm.[69] In a neoadjuvant trial of bevacizumab and chemotherapy in patients with inflammatory breast cancer, in which at least 4 weeks were required from the last dose of bevacizumab before surgery, 5 of the 21 patients developed wound complications, including prolonged seromas, dehiscence, and delay in primary wound closure.[73]

Current guidelines are largely empiric and recommend that bevacizumab be withheld for 4 weeks before elective surgery. As the half-life for small-molecule TKIs is typically short, a 'wash out' period of 1 week is recommended in most trials. At this time, for both mAbs and TKIs that target the VEGF pathway, several neoadjuvant trials are ongoing, which will provide more evidence-based guidance in the future.

Brain complications such as RPLS

RPLS (posterior reversible encephalopathy syndrome) is a clinicoradiological entity associated with capillary leak and vasogenic edema in the brain.[74,75] Noncontrast MRI is the key to diagnosis. Typical features are hyperintensity in the T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequences, with primary involvement in the white matter of posterior parietal and occipital lobes, and to a lesser extent, in the gray matter and the anterior distributions. Severe RPLS can lead to cerebral hemorrhage or ischemia.

RPLS is recognized as a rare adverse effect (affecting <1% of patients) of VEGF/VEGFR inhibitors, and has been reported in patients treated with bevacizumab,[24,76,77] sorafenib,[67,78] or sunitinib.[31,79] Other cancer therapies, such as interferon alpha, granulocyte colony-stimulating factor, cyclosporine, cisplatin, and capcitabine, have also been reported to cause RPLS.[74,75] Clinical features of RPLS associated with VEGF/VEGFR inhibitors in individual cases are variable in severity, degree of blood pressure elevation, and onset. Presentations can range from headache and nonspecific mental status change, to seizure, cortical blindness, or other complications such as stroke or hemorrhage. Blood pressure is elevated from baseline in most, but not all, patients; severe hypertension or hypertensive crisis is present in only a subset of cases. The onset of RPLS can occur within 24 h to months after anti-VEGF therapies. The clinical course is reversible in most patients after cessation of therapy; however, in rare cases, residual neurological deficits are present.[80]

RPLS should be considered as part of the differential diagnosis in patients on anti-VEGF therapy presenting with nonspecific CNS symptoms, including headache and mental status change; MRI is required to clarify the diagnosis. Timely correction of the underlying causes, including control of blood pressure and interruption of the causative drug, is important to prevent irreversible tissue damage. The safety of resuming VEGF/VEGFR inhibitors after recovery from RPLS is unknown.

Other adverse events

Hematological adverse events

VEGFRs are expressed on hematopoietic cells and EC precursors,[81] and they have a role in both erythropoiesis and myelopoiesis. Therefore, it is conceivable that myelosuppression could occur as a result of VEGF inhibition. However, myelotoxicity has not been associated with bevacizumab monotherapy. On the other hand, anti-VEGF TKIs are myelosuppressive; for example, sunitinib is known to cause both neutropenia (all grades, 43–72%; grade 3, 8–11%) and thrombocytopenia (all grades, 36–65%; grade 3, 4–8%).[20,21] Sorafenib is also associated with neutropenia (all grades, 18%; grade 3–4, 5%)[67] and thrombocytopenia (all grades 12%; grade 3–4 1%).[67]

The difference in myelosuppressive effect observed between bevacizumab and VEGFR TKIs is not fully understood. It is possible that blockage of VEGF-A only by bevacizumab is not sufficient to induce clinically evident myelosuppression and that simultaneous inhibition of additional targets, such as c-KIT (a target of sunitinib and sorafenib) is required. Another possibility might be related to the potential role of the internal VEGF/VEGFR autocrine loop in hematopoiesis, which was reported by Gerber *et al.*[82] In that study, *VEGF* deletion and VEGFR TKIs had a similar effect in reducing the colony formation of hematopoietic stem cells, while a soluble VEGFR1 that acted in an extracellular manner had little effect. These results suggest that an autocrine loop mediated by intracellular VEGF and VEGFR might be responsible for hematopoietic cell survival, and that this signaling would not be affected by neutralization of extracellular VEGF by bevacizumab.

Venous thromboembolism

The association between venous thromboembolism and VEGF/VEGFR inhibitors is less clear than the association of ATEs with these agents. In a pooled analysis of five randomized trials that included 1,745 patients, the rate of grade 3 to 4 venous thromboembolism was not increased (9.97% versus 9.85%).[26] On the other hand, a meta-analysis of 13 randomized trials, which included a total of 7,656 patients, indicated a small increase in grade 3 or above venous thromboembolism (6.3% versus 4.2%) in those receiving anti-VEGF agents, although the difference was not statistically significant.[83]

Table 7 | Myelosuppression and neuropathy observed in trials of bevacizumab and sorafenib combined with chemotherapy

Treatment regimen	Tumor type	*n*	Adverse event	Grade	Incidence of AE in chemotherapy arm (%)	Incidence of AE in combination arm (%)
IFL ± bevacizumab	CRC[24]	813	Neutropenia Thrombocytopenia	Grade 3–4 Grade 3–4	14 0	21 5
FOLFOX ± bevacizumab	CRC[47] (E3200) CRC[70] (NSABP C-08)	829 2,710	Sensory neutropathy Sensory neutropathy	Grade 3–4 Grade ≥2 Grade ≥3	9 43.7 14.4	17 48.9[a] 16.7
Paclitaxel (weekly) ± bevacizumab	Breast[46] (E2100)	722	Neutropenia Thromobcytopenia Sensory neuropathy Infection	Grade 3–4 Grade 3–4 Grade 3–4 Grade 3–4	0.3 0.3 17.1 2.9	0 0 24.5[b] 9.3[c]
Paclitaxel-carboplatin ± bevacizumab	NSCLC[48] (E4599)	878	Neuropenia Thromobcytopenia Febrile neutropenia	Grade 4 Grade 4 Grade 3 Grade 4 Grade 5	16.8 0.2 1.8 0 0.2	25.2[d] 1.6[e] 4[f] 0 1.2
Dacarbazine ± sorafenib	Melanoma[63]	101	Neuropenia Thrombocytopenia	All Grade 3–4 All Grade 3–4	22 12 35 14	45 33 59 18
Paclitaxel-carboplatin ± sorafenib	Melonoma[101]	270	Neuropenia Thrombocytopenia	Grade 3–4 Grade 3–4	46 12	49 28

[a]$P < 0.01$. [b]$P = 0.05$. [c]$P < 0.001$. [d]$P = 0.002$. [e]$P = 0.04$. [f]$P = 0.02$. Abbreviations: AE, adverse event; CRC, colorectal cancer; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; IFL, irinotecan, fluorouracil and leucovorin; NSCLC, non-small-cell lung cancer.

Limited data on venous thromboembolism are available for VEGFR TKIs. Venous thromboembolism has so far not been associated with sorafenib treatment in trials of HCC, RCC or melanoma.[18,19,63] In a phase III trial of sunitinib or placebo in patients with RCC, the rates of venous thromboembolism were 2% in both arms. In a randomized trial in patients with GIST treated with sunitinib versus placebo, venous thromboembolism was 3% versus 0% for all grades and 2.5% versus 0% for venous thromboembolism greater than grade 3.[31]

Considering the inherent rate of venous thromboembolism related to cancer and chemotherapy, a small increase in risk as a result of anti-VEGF agents would require a large sample size to achieve statistical significance. Further evaluation is warranted. With the current knowledge, patients with venous thromboembolism are not excluded from treatment with anti-VEGF therapies.

Hypothyroidism

Preclinical data have indicated that VEGF inhibition can rapidly reduce fenestration in endocrine organs, including the thyroid gland, adrenal cortex and pituitary gland.[84] VEGF may also stimulate thyroid cell growth. In addition, multitargeted agents might inhibit thyroid function through simultaneous blockage of additional pathways to VEGF. In clinical studies, sunitinib induces hypothyroidism in 36% of patients.[85] However, hypothyroidism has not been associated with bevacizumab, and was uncommon in patients treated with sorafenib.[67] It seems that the role of VEGF in thyroid function is complex, and an association between VEGF inhibition and hypothyroidism is uncertain.

Anti-VEGF agents in combination regimens

Combination regimens with chemotherapy

Both bevacizumab and VEGFR TKIs may potentiate chemotherapy-related adverse events, although the risk varies with the clinical setting and the chemotherapy backbone. Bevacizumab or sorafenib in combination with chemotherapy regimens was associated with an increased high rate of neutropenia and thrombocytopenia, except in the E2100 trial where bevacizumab was combined with weekly paclitaxel (Table 7). When the chemotherapy regimens are neurotoxic, such as FOLFOX and paclitaxel, the addition of bevacizumab also increases the rate of sensory neuropathy (Table 7).[46,47]

Serious to life-threatening adverse events may also be increased with the combination regimen of chemotherapy and antiangiogenesis agents, particularly in some clinical settings or groups of patients. In the pivotal phase III trial (E4599) in patients with metastatic NSCLC, the rate of grade 3 or higher neutropenia with fever or infection was increased in the combination arm with bevacizumab plus carboplatin and paclitaxel compared with chemotherapy alone (5.2% versus 2%), and more patients in the bevacizumab-containing arm died from neutropenic infection (5 versus 1).[48] In that trial, the relative increase in serious adverse events associated with the combination regimen was even more significant in elderly patients (>70 years of age), and negated the survival benefit in this subgroup despite an improvement in tumor response and progression-free survival by the addition of bevacizumab.[86]

A number of randomized trials for VEGFR TKIs (including sorafenib, cediranib and motesanib) in combination

with chemotherapy as first-line treatment in metastatic NSCLC have reported increases in treatment-related mortalities as a result of serious infection, cytopenia or hemorrhage.[59,61,87] The excessive toxicities observed in these trials have necessitated modifications of the trial for dose reduction[88] or changes in patients' entry criteria.[61]

Combination of two antiangiogenesis agents

Given the complexity of angiogenesis and its compensatory mechanisms, combining more than one antiangiogenic agent has generated great interest. Nonetheless, trials have shown that adverse effects were significantly enhanced when agents targeting the same pathway were combined, and dose reduction was required in many cases. In phase I trials of sorafenib combined with bevacizumab, hypertension, hand-foot syndrome, and proteinuria occurred with earlier onset, higher frequency, and greater severity compared with either agent alone.[89] Dose reductions of 50% for bevacizumab (that is, reducing the dose to 5 mg/kg every 2 weeks) and sorafenib (to 200 mg twice daily) plus sorafenib drug holidays (2 of 7 days) were necessary and determined to be the MTD for the combination.[90] Further dose reductions were required in almost all patients after 4 months of therapy. In patients with RCC, the MTD was even lower (sorafenib 200 mg daily with bevacizumab dose 5 mg/kg every 2 weeks).[90]

The combination of sunitinib and bevacizumab was also associated with dose-limiting hypertension, thrombocytopenia, and proteinuria. Although full doses of both agents (bevacizumab 10 mg/kg every two weeks and sunitinib 50 mg daily for 4 out of 6 weeks) were determined to be the MTD based on the safety profile of one cycle, prolonged therapy for multiple cycles in patients with RCC led to development of microangiopathic hemolytic anemia, with associated grade 3–4 hypertension, thrombocytopenia and proteinuria in 5 of 12 patients assessed.[55]

Bevacizumab in combination with mammalian target of rapamycin (mTOR) inhibitors, such as temsirolimus or eversirolimus,[91,92] seems to be well tolerated at the full doses of both agents. Further studies in additional patients, however, are needed to fully establish the safety profile of these combinations. On the basis of preliminary observations of promising antitumor activities—despite the requirement of dose reduction for some regimens—further combination studies are ongoing. At this time, however, no proven benefit for combining antiangiogenesis agents has been demonstrated, and these regimens should only be used in the setting of clinical trials.

Conclusions and future directions

With the expanding use of antiangiogenesis agents such as bevacizumab, sorafenib, and sunitinib in standard practice, the diverse adverse effects of this class of agents have become increasingly recognized. Although most of the adverse events are manageable, life-threatening and fatal complications can occur. Combining these agents with chemotherapy or other targeted agents can further increase the incidence and severity of adverse events.

Most of the currently available safety data for antiangiogenesis agents are derived from controlled clinical trials that commonly excluded patients with significant cardiac risk factors (such as ATEs or CHF within 6 or 12 months, or uncontrolled hypertension), nonhealing wounds and other tumor-related or comorbid conditions; the duration of therapy and follow-up were also short because of rapid tumor progression in the metastatic setting. Treatment might conceivably be associated with more significant adverse effects in patients with preexisting morbidities. Careful risk–benefit assessment for individual patients is important, and should take into account risk factors related to the host and the tumor, as well as the concurrent agent(s) in combination with the antiangiogenesis agents.

At the current time, approaches to toxicity management and treatment modifications are largely empirical. In order to provide evidence-based guidance for more-effective risk identification and mitigation, therapeutic or observational studies could be designed with the following primary or ancillary goals: identify baseline risk factors and early signs of serious adverse events; document the choice of interventions and their effectiveness for selected toxicities; and collect data on safety should antiangiogenesis agents be resumed after recovery from adverse effects.

Finally, a critical task for the field is correlative studies to identify predictive markers for efficacy and toxicity. As antiangiogenesis therapies primarily target nontumor cells, one of the areas of great interest is pharmacogenomic studies to examine the potential relationship between the genetic background of the host and the therapeutic and/or adverse effects of the agents. To that end, exploratory studies are ongoing for germline single nucleotide polymorphism analyses. Currently, no predictive biomarkers are available for toxicity or efficacy for anti-VEGF therapies. Additional work should continue to explore both host- and tumor-related biomarkers in ongoing or completed clinical trials, and to validate promising leads in independent datasets.

Review criteria

Information for this Review was prepared by searching the PubMed database for articles published before 10 January 2009. The search terms included, but were not limited to, "antiangiogenesis," "bevacizumab," "sorafenib," "sunitinib," "randomized clinical trial," and "toxicity." When possible, toxicity data were taken from publications regarding controlled randomized trials; however, data were also obtained from case reports and meta-analyses. Additional information was obtained from published meeting abstracts, pharmaceutical agent package inserts, pharmaceutical company press releases, and www.clinicaltrials.gov.

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