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Antiangiogenic Therapy: Tolerability and Management of Side Effects

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Therapies that attack a tumor's blood supply (antiangiogenesis) are transforming the treatment of cancers of the liver, kidney, and gastrointestinal tract, among others. Antiangiogenic agents target the blood supply to tumors, primarily by blocking the actions of angiogenic growth factors and their signaling pathways. VEGF (vascular endothelial growth factor) and PDGFR (platelet-derived growth factor receptor) were the first validated angiogenic targets, but many others are being targeted by newer therapies. Bevacizumab (BV; Avastin®), the first specifically designed antiangiogenic cancer agent, is a humanized monoclonal antibody that binds circulating VEGF, thus preventing the ligand from acting on the receptor. Two other approved agents, sorafenib (Nexavar®) and sunitinib (Sutent®), are orally administered small molecule tyrosine kinase inhibitors (TKIs) that disrupt intracellular angiogenic signaling by binding competitively to the ATP binding sites on receptors for VEGF and other growth factors.

Antiangiogenic therapies are generally well tolerated compared to traditional cytotoxic chemotherapy agents, primarily because they are more selective in their cellular effects. Nonetheless, they are associated with a variety of distinct side effects that require monitoring and management. The TKIs cause a wider range of side effects than antibody therapy due to their broader activity beyond angiogenesis inhibition. In clinical trials of sunitinib, the most frequently reported toxicities were diarrhea, hypertension, fatigue, and nausea, while for sorafenib they were diarrhea, skin toxicities, and alopecia[1]. BV is most often associated with hypertension and proteinuria (excess protein in the urine), followed by mild thrombotic and bleeding events. Other notable but infrequent side effects with BV therapy include serious (grade 3-4) bleeding, arterial thromboembolism, wound healing complications, GI perforation, and nephrotic syndrome[2]. This article reviews the major classes of side effects of antiangiogenic therapies and their management.

Cardiovascular Side Effects

Hypertension

Hypertension is a common class-based side effect of VEGF inhibitors and is also one of the most manageable using standard blood pressure medications. Under normal conditions, VEGF regulates synthesis of the vasodilator nitric oxide (NO) in vessel walls by upregulating production of endothelial NO synthase (eNOS). Inhibiting VEGF decreases NO production, promoting vasoconstriction, increased peripheral resistance, and elevated blood pressure[3]. Anti-VEGF therapy also induces a functional decrease in the number of arterioles and capillaries, which may also contribute to increased peripheral resistance[3]. The effects of VEGF inhibition in the kidneys is also associated with the development of hypertension in some patients[3]. In phase 3 trials in metastatic colorectal cancer (mCRC), 11-16% of patients treated with first-line BV and chemotherapy developed grade 3 hypertension requiring aggressive medical therapy[3]. However, the true incidence may be considerably higher depending on the chemotherapy that is paired with BV and the hypertension criteria used[4]. In pivotal studies of sunitinib and sorafenib for metastatic renal cell carcinoma (mRCC), grade 3-4 hypertension was reported in 4.0% and 3.0% of patients, respectively, for the two agents[4]. Blood pressure elevation in cancer patients initiated on antiangiogenic therapy can occur rapidly, as illustrated by a retrospective analysis of 14 consecutive patients with mRCC who received sunitinib 50 mg/day (4 weeks on, 2 weeks off)[5]. Among patients who were normotensive at baseline (n = 7), the authors reported significant spikes in blood pressure during on-therapy periods, often within the first week of treatment (mean [±SD] increase in systolic BP, 13.6±8.4 mm Hg; mean increase in diastolic BP, 10.9±4.7 mm Hg). Blood pressure increased steadily thereafter, so that all patients were hypertensive by week 4 on treatment. Patients with a prior history of hypertension had much less dramatic increases, most likely because they were already on antihypertensive medications. Notably, the blood pressure spikes were detected by home measurement between office visits, suggesting the need for close monitoring of blood pressure by home measurement in patients initiated on sunitinib[5].

Because hypertension may be an early and insidious potential sign of cardiotoxicity, prompt intervention is essential to avoid potentially irreversible damage to the heart. Prospective trials defining optimum antihypertensive therapy for patients receiving VEGF inhibitors are presently lacking, but recent findings suggests that aggressive preemptive treatment with an angiotensin-converting enzyme (ACE) inhibitor and/or beta-blocker may be necessary at the initiation of, or early in the course of sunitinib therapy[6]. Of interest, angiotensin 2 is a potent proangiogenic growth factor, which makes it an intriguing target in cancer patients. ACE inhibitors and angiotensin 2 receptor antagonists (ARAs) have demonstrated both antineoplastic and antiangiogenic activity in experimental tumor research, and studies are underway to assess whether these agents may have clinical utility in cancer treatment[4]. Anti-hypertensive agents that affect NO regulation may also be useful for patients on anti-VEGF therapies. These include the long acting oral nitrates, such as sildenafil, and nebivolol, a beta-blocker that

From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this issue of *Targeting Tumor Angiogenesis: Tolerability and Management of Side Effects.* Three preeminent experts, Dr. Mario E. Lacouture, Daniel J. Lenihan, and Susan E. Quaggin, discuss the latest evidence on the tolerability of antiangiogenic cancer therapies and the clinical management of side effects.

– *William W. Li, M.D., President*
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also acts as a vasodilator. The blood pressure lowering effect of nebivolol is mainly related to a reduction in peripheral resistance, making it a good option for patients on anti-VEGF therapy[1].

Acute hypertension in patients on anti-VEGF therapy has been linked to reversible posterior leukoencephalophathy (RPLS), a rare but serious brain syndrome associated with disturbed regulation of the cerebral vasculature and dysfunction of the blood brain barrier, resulting in vasogenic edema[7]. Symptoms of RPLS include headache, seizures, lethargy, confusion, and visual disturbances. MRI of the brain typically shows white matter edema primarily of the parietal and occipital regions, which is reversible with removal of the causative agent[7]. At least 9 cases of RPLS have been reported in patients on BV therapy, and at least one case each with sunitinib and sorafenib[7, 8, 9]. In a recent report, a patient with mRCC receiving sunitinib 50 mg/day developed symptoms of RPLS, which was confirmed by MRI 7 days after initiating therapy[9]. At the time of diagnosis, the patient's blood pressure was elevated at 190/130 mm Hg. Three days after discontinuation of sunitinib and initiation of antihypertensive medication, the patient's headache and neurological symptoms resolved. A follow up MRI showed completed resolution of white matter changes. This case report highlights the importance of early, aggressive treatment of hypertension, with discontinuation of anti-VEGF therapy if RPLS is suspected.

LVEF decline and heart failure

A decline in left ventricular ejection fraction (LVEF) has preceded the development of heart failure (HF) in patients on sunitinib, particularly in those with a prior history of coronary artery disease. In a retrospective study of 75 patients with imatinib-resistant, metastatic gastrointestinal stromal tumors (GIST) who received sunitinib at or below the approved dose (50 mg/day, 4 weeks on, 2 weeks off), cardiac events were reported in 8 (11%) patients[10]. Six of these patients developed heart failure. Of 36 patients who were treated with the approved sunitinib dose, most had a reduction in LVEF from baseline, while 2 (6%) had LVEF reductions of 20% ejection fraction (EF) and 7 (19%) had reductions of 15% EF[10]. In this series, a prior history of coronary artery disease was the only significant independent predictor of heart failure (OR 16.8; P=0.012). In addition, 6 of 36 patients (17%) developed grade 3 hypertension by the third sunitinib cycle. Left ventricular dysfunction and symptoms improved in 5 of 6 patients with HF after sunitinib therapy interruption, dose modification, initiation of HF medication, or a combination of these measures.

Examination of endomyocardial biopsy samples from HF patients in the study, as well experimental studies of sunitinib treatment in mice and rats, revealed evidence of mitochondrial damage in cardiomyocytes[10]. The researchers therefore propose that some contractile dysfunction in patients on sunitinib therapy could result from the loss of ATP generation secondary to mitochondrial injury. The role of hypertension in the development of HF in patients receiving sunitinib also needs further examination. A one-year retrospective study of sunitinib and heart failure conducted at the M.D. Anderson Cancer Center Cardiology Department identified 6 of 224 (2.7%) patients who developed symptomatic heart failure shortly after initiating sunitinib therapy (mean onset 22 days after therapy initiation), which was not completely reversible in most patients, even after sunitinib discontinuation[6]. Notably, all HF patients had hypertension or elevated blood pressure at baseline and during treatment with sunitinib. Similar findings were reported from a retrospective study conducted at Stanford, and the observed incidence of grade 3-4 HF in carefully monitored patients was considerably higher, at 15%, emphasizing the need for aggressive treatment of hypertension with agents useful in preventing HF[11].

These findings, combined with past experience with cardiotoxicity in cancer patients receiving certain chemotherapies, underscore the importance of early and routine monitoring of cardiac function in patients initiated on sunitinib[10, 12]. Multiple gated acquisition (MUGA) and echocardiography are the most common methods of assessing cardiac function during cancer treatment. Because the myocardium has substantial compensatory reserve, however, LVEF often underestimates and can actually mask the actual extent of damage to cardiomyocytes[13]. Clinical investigations are therefore underway to evaluate novel imaging techniques, as well as possible serum-based biomarkers, to detect early, subclinical changes in cardiac function that may occur during many forms of cancer treatment. Newer imaging modalities include Doppler echocardiography to assess tissue and blood flow velocities and strain rate, MRI combined with late gadolinium contrast enhancement, and targeted nuclear imaging[12].

Thrombosis and bleeding

It is well established that cancer patients have an inherently higher risk of thrombosis than healthy individuals. The release by tumor cells of pro-thrombotic factors into the circulation, side effects of some chemotherapy agents, and the higher prevalence of underlying cardiovascular disease in elderly patients predispose cancer patients to thrombosis. Anti-VEGF therapy, particularly BV, is also associated with an increased incidence of thrombosis. Although the reasons for this are not entirely clear, physiological VEGF at very low concentrations is required for the repair and maintenance of the capillary endothelial cell lining in response to injury, such as occurs in patients with cardiovascular disease[14]. The endothelial cell lining of tumor vessels is also sensitive to fluctuations in VEGF levels. Pharmacological inhibition of VEGF may increase endothelial cell apoptosis, which may disturb the endothelial lining and expose underlying pro-coagulant factors[3].

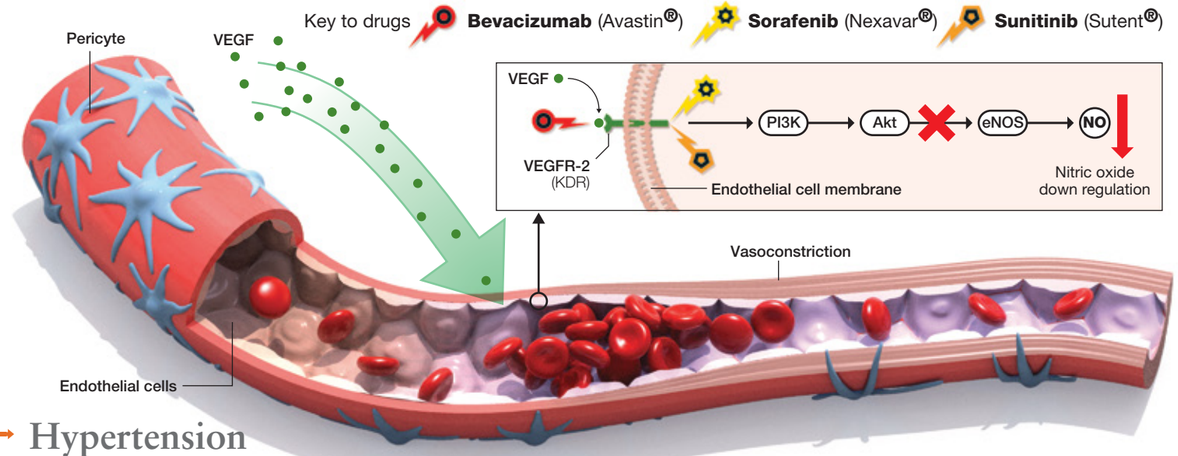
The incidence of both arterial and venous thrombotic events is increased in patients on BV therapy. In a meta-analysis of 5 clinical trials in mCRC, non-small cell lung cancer (NSCLC), and advanced breast cancer, the addition of BV to chemotherapy approximately doubled the overall incidence of arterial thromboembolic events (ATEs)—from 1.7% for chemotherapy alone to 3.8% for chemotherapy plus BV[2]. Patients ≥ 65 years of age and those with a history of prior thrombosis had a higher increased risk (P=0.01 and P<0.001, respectively)[2]. Because the safety of resuming BV therapy in patients with a resolved ATE has not been studied, BV prescribing information states that the agent should be discontinued in patients who experience a severe ATE[15]. The risk of venous thromboembolism (VTE) with BV treatment is less established. While the same study found no increased risk for VTE with BV therapy, a more recent meta-analysis of 15 randomized, controlled trials of BV for a variety of solid tumors found a significantly higher risk of VTE for BV-treated patients compared with controls (RR, 1.33; P<0.001), both at the 2.5 and 5 mg/kg doses[16]. The VTE rate varied significantly by tumor type—from 3.0% in RCC patients to 19.1% in CRC patients (overall incidence, 11.9%). The rates of grades 3-5 VTE were 6.3% overall, and 2.0% and 7.3% for RCC and CRC, respectively.

Paradoxically, the diminished maintenance and repair capacity of the endothelial cells lining blood vessels resulting from VEGF inhibition can also induce bleeding[2]. Most bleeding complications in patients on BV therapy are mild, such as self-limiting nosebleeds, but serious bleeding events can occur, though infrequently[2]. The use of BV in patients with NSCLC of squamous cell histology is specifically contraindicated following fatal pulmonary hemorrhage in a phase 2 trial[2, 15]. In mCRC clinical trials, grade 3-4 bleeding occurred at an overall incidence of 3.0-5.0% with BV, compared with 2.5-3.0% with chemotherapy alone[2]. In BRiTE, a cohort study of 1,953 mCRC patients treated with first-line BV and chemotherapy, 2.6% developed a grade 3-4 bleeding event, with a median time to occurrence of 6 months from the first BV dose[17]. More than half of these (55.8%) were GI-rectal bleeding events. Patients with a primary tumor of the rectum had a higher incidence than those with a primary tumor of the colon (4.0% vs. 2.0%, P=0.012). Grade 3-4 bleeding events, however, were not significantly increased in patients on prophylactic anticoagulant therapy (2.9%) compared to those who were not (2.2%), but were increased in patients receiving both anticoagulant and antiplatelet medications (7.2%). In a second prospective observational study of first-line BV plus chemotherapy for mCRC, First-BEAT, 2.7% of patients experienced a grade 3-4 bleeding event, including one serious nosebleed[18]. Low-grade bleeding complications have also been reported in up to 26% of patients treated with sunitinib and up to 60% of patients treated with sorafenib[14].

The vasculature of healthy adults is not dependent on VEGF, as angiogenesis occurs mainly during fetal development. Certain organs, however, including the heart and kidneys, require tightly controlled, very low levels of VEGF to maintain healthy vascular beds and function normally. Disruption of the supply of VEGF and other proangiogenic growth factors to these blood vessels by antiangiogenic therapies can result in a number of adverse effects involving these organ systems. Because many cancer patients are elderly or have pre-existing underlying conditions, they are inherently more susceptible to adverse effects of antiangiogenic therapy, and therefore require careful monitoring and management.

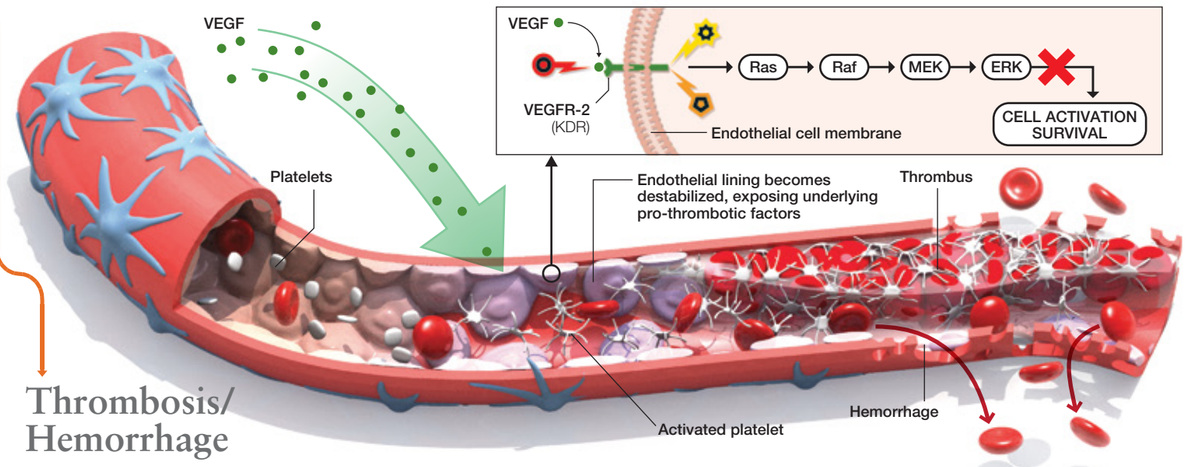
Heart

Kidneys



Hypertension

VEGF plays a key role in maintaining normal vascular tone by regulating production of nitric oxide (NO), a vasodilator, by arterial endothelial cells. Hypertension may result when anti-VEGF therapy decreases NO production, causing vasoconstriction and increased peripheral resistance. Patients with a prior history of hypertension are at the greatest risk for developing this side effect.



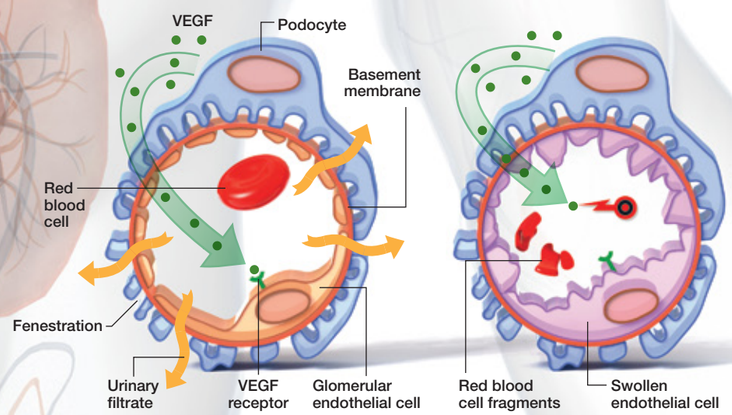
Thrombosis/ Hemorrhage

People with cancer are at higher risk of thrombosis than the general population due to a number of complex factors that are not entirely clear. Cancer patients' pro-thrombotic state may be further exacerbated by anti-VEGF therapy. Paradoxically, antiangiogenic therapy also leaves capillaries susceptible to secondary hemorrhage by interfering with repair of the endothelial cell lining, which is very sensitive to VEGF inhibition in its injured state. Tumor capillaries and blood vessels of patients with atherosclerosis, peripheral vascular disease, and diabetes are therefore particularly vulnerable to thrombosis/hemorrhage with antiangiogenic therapy.

Renal Side Effects

A VEGF produced by podocytes, modified pericytes, is required for the health and maintenance of the adjacent glomerular endothelium. Fenestrations in glomerular endothelial cells allow urinary filtrate to pass from the blood lumen to the urinary space.

B Renal abnormalities in patients receiving antiangiogenic therapy may result from a loss of VEGF production by podocytes, leading to microvascular injury, thrombotic microangiopathy, and reduced permeability (loss of fenestrations) of the glomerular filtration barrier.



Heart Failure

Cancer patients receiving antiangiogenic therapy, particularly those with pre-existing cardiovascular disease, appear to be at increased risk for left ventricular dysfunction and heart failure. While uncontrolled hypertension likely plays a role in the development of these conditions, recent experimental studies suggest that anti-VEGF therapy, particularly sunitinib, may activate the mitochondrial apoptotic (programmed cell death) pathway in cardiomyocytes. Myocyte death and ATP depletion could therefore possibly contribute to contractile dysfunction and heart failure.

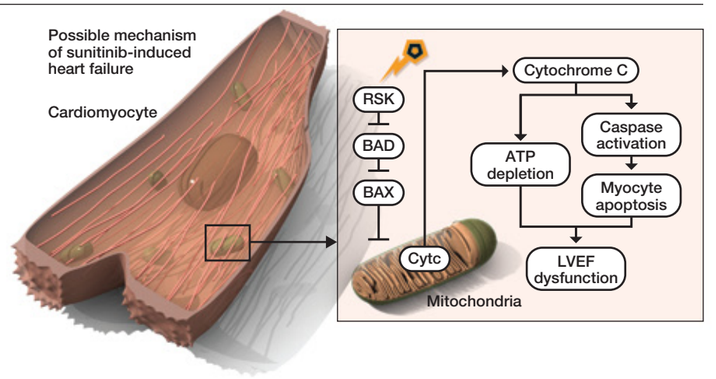


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Diagram by Bryan Christie Design.
Illustration consultant, Giannoula Klement, M.D.

Delayed Wound Healing/GI Perforation

Because angiogenesis is required for wound healing, VEGF inhibition could theoretically interfere with normal angiogenesis and healing of the intestinal mucosa and the liver following tumor resection[2]. An increase in post-surgical wound healing complications, including wound dehiscence and impaired wound healing, has been reported with BV treatment for mCRC[2]. In the observational BRiTE mCRC study, grade 3-4 post-operative wound healing complications occurred in 3.7% of patients who underwent surgery of any kind after initiating BV treatment[2, 18]. Patients who underwent major abdominal surgery or who had surgery within 14 days of their last BV dose had a higher risk (7.0%). A recent retrospective analysis of mCRC patients who received neoadjuvant BV plus chemotherapy prior to resection of liver metastases, however, found no significant increase in post-operative hepatobiliary or wound complications compared with chemotherapy alone[19]. The time from the last BV dose to surgery also had no impact on the rate of post-surgical complications. Until prospective studies are completed, current recommendations state that BV should be discontinued 60 days prior to surgery and reinstated 28 days following surgery to avoid surgical complications, even though wound angiogenesis is generally established by 7-10 days after incision closure[2, 15, 19].

Gastrointestional (GI) perforation is another infrequent but serious complication associated with BV[20]. A recent meta-analysis of 17 randomized, controlled trials of BV therapy for a variety of solid tumor types found an overall incidence of GI perforation of 0.9%, with a mortality rate of 21.7%[20]. The risk of GI perforation was significantly increased in all patients with mCRC (RR, 3.68; P=0.016), and particularly in mCRC patients who received BV 5 mg/kg per week (RR, 6.95). However, the overall relative risk of GI perforation across all studies was quite low (RR, 2.14). In patients who received BV 2.5 mg/kg per week, the relative risk was only 1.61. GI perforation was reported in 2.0% of patients receiving BV in both BRiTE and First BEAT, although the reporting criteria were less stringent in these registries than in the randomized, controlled trials[18]. Intact primary tumor, acute diverticulitis, intra-abdominal abscess, gastric ulcer, GI obstruction, abdominal carcinomatosis, and prior abdominal or pelvic radiation are potential risk factors for GI perforation with BV treatment for CRC[21]. BV should be used with caution in patients with one or more of these risk factors and permanently discontinued if perforation occurs. Prophylatic therapy with proton pump inhibitors may be advisable for patients with a history of gastric ulcer initiating BV therapy[21]. Wound healing complications and GI perforation have not been widely reported in patients treated with TKIs, but this may be attributable to the lack of data with these agents for these complications[14].

Renal side effects

Proteinuria is one of the most common side effects of BV therapy, with an overall incidence ranging from 21-64% in a dose-dependent manner[22]. Grade 4 proteinuria (nephrotic syndrome) occurs in only 1-2% of BV-treated patients, but denotes structural damage to the glomerular filtration barrier, which may be irreversible[2, 22]. In a meta-analysis of 7 clinical trials of BV involving various cancer types, 6 of 597 patients (1.0%) developed grade 3 proteinuria (protein >3.5 g/24h) with low doses of BV (3-7.5 mg/kg), and 7 of 381 (1.8%) with high-dose BV (10-15 mg/kg)[23]. The relative risk of developing proteinuria was significantly elevated with both low-dose BV (RR, 1.4; *P*=0.003) and high-dose BV (RR, 2.2; P<0.001) compared to placebo controls. A recent report described 6 cases of renal thrombotic microangiopathy in patients receiving BV for various cancer types at doses ranging from 7.5 to 15 mg/kg[22]. Patients developed proteinuria ranging from 160 mg/24 hours (grade 1) to 4613 mg/24 hours (grade 3-4). Onset was as soon as 3 months after treatment initiation to as late as 9 months. Three of 6 patients had grade 3 acute kidney injury with a tripling of baseline creatinine.

Although the precise mechanisms of renal toxicity with BV therapy are not fully understood, basal VEGF at low levels is essential for the healthy maintenance of the adjacent glomular endothelium; disruption of the VEGF supply results in thrombotic microangiopathy localized to the kidney[22]. In contrast to studies in mice, in which BV treatment causes complete and irreversible loss of VEGF production in the kidneys, its effects in humans appear to be primarily transient–renal function, proteinuria, and blood pressure changes are reversible and usually improve when the drug is withdrawn[22]. There is also a clinical association between proteinuria and hypertension in patients treated with BV, although a causal relationship has not been established[24].

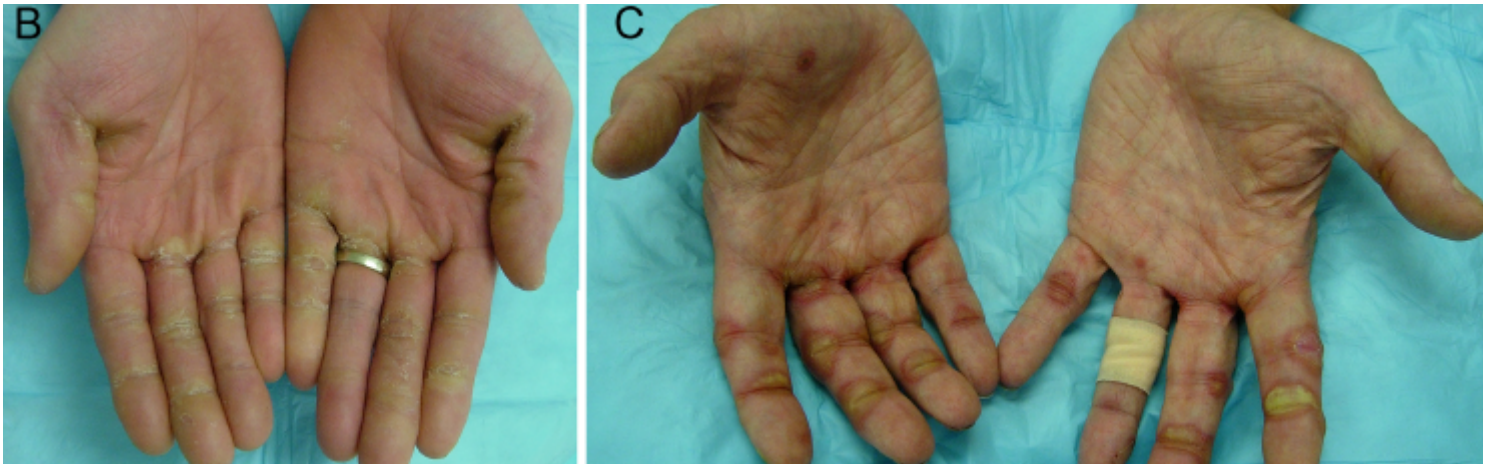
The role of VEGF in patients with pre-existing glomerular damage, such as those with diabetes mellitus, appears to be important. VEGF expression increases in patients with early diabetic nephropathy, possibly as an injury response, so its inhibition may therefore exacerbate pre-existing kidney damage and increase the risk for proteinuria[2]. While there are currently no standard screening recommendations for proteinuria in patients on BV therapy, urinary dipstick, 24-hour urine collection, and urine protein/creatinine ratio are used for diagnosis of nephropathy associated with diabetes and hypertension[2]. A blood smear is also useful for detection of shistocytes, fragmented red blood cells, and thrombocytopenia, both of which are markers of thrombotic microangiopathy. Given the association between proteinuria and hypertension in patients on anti-VEGF therapy, it is recommended that medical management include an agent directed at both conditions, such as an ACE inhibitor or angiotensin receptor blocker, which are both anti-hypertensive and renal-protective[24]. Second-line, add-on therapies to treat hypertension could include non-dihydropyridine calcium-channel blockers, aldosterone receptor antagonists, or rennin inhibitors[2].

Hypothyroidism

Hypothyroidism, defined as a low level of serum T4 and an elevated level of serum thyroid stimulating hormone (TSH), has been observed primarily with sunitinib therapy and may contribute to the high incidence of fatigue associated with this agent[25]. Phase 2 studies of sunitinib for mCRC, NSCLC, and metastatic breast cancer have documented fatigue/athenia, the most frequent symptom of hypothyroidism, in 53-70% of patients (grade 3-4,14-29%)[25]. Constipation and dry skin consistent with hypothyroidism were observed in 12-24% and 11%, respectively. In a prospective study of sunitinib 50 mg/day in 59 patients with mRCC or imatinib-resistant GIST, 20 (34%) had transient elevation of TSH not requiring therapeutic intervention, and 16 (27%) developed subclinical or clinical hypothyroidism requiring medical intervention[26]. All patients in the study had normal TSH levels at baseline.

Intriguingly, in another prospective study, mRCC patients who developed thyroid abnormalities while on sunitinib had significantly prolonged progression-free survival compared with those who did not (10.3 vs. 3.6 mo., *P*=0.47)[27]. These findings suggest that inter-patient variability in the pharmacokinetics of sunitinib could impact clinical outcome. Alternatively, there is also some evidence that hypothyroidism itself may suppress tumor growth. Preclinical studies have shown that thyroid hormone induces tumor growth and angiogenesis via a plasma membrane hormone receptor on integrin $\alpha_v\beta_3$, which is present on both tumor and endothelial cells[25]. Several studies have documented improved survival for cancer patients with treatment-induced hypothyroidism, although this observation requires further study.

The mechanism of sunitinib-induced hypothyroidism is unclear, but may involve regression of thyroid capillaries due to VEGFR inhibition. Experimental studies in mice have shown that thyroid tissue exhibits the greatest degree of capillary regression of any organ during VEGF suppression[3]. The capillaries regenerate when the VEGF inhibitor is removed—a phenomenon some researchers say could explain the rhythmic pattern of TSH levels observed in patients treated with sunitinib administered in the 4/2 dosing schedule[26]. While optimum medical management of hypothyroidism in patients on sunitinib is not yet established, thyroid function tests (measurement of serum TSH and T4 levels) are recommended at baseline and on day 1 and 28 of the first 4 treatment cycles[26]. In patients with persistent elevated TSH (>10 mU/l) and either low T4 or normal T4, but with typical symptoms of hypothyroidism, initiation of hormone replacement therapy is recommended[26].



Examples of grade 2 (B) and grade 3 (C) hand-foot skin reaction with sorafenib.

Dermatologic Side Effects

Hand-foot skin reaction

Suntinib and sorafenib are associated with a number of primarily mild dermatologic side effects, of which hand-foot skin reaction (HFSR) is one of the most common. Patients with HFSR develop thick, well-defined hyperkeratotic lesions affecting friction- and weight-bearing surfaces, primarily on the hands and feet, and which are often accompanied by pain, numbness, tingling, and dry and/or cracked and peeling skin[1]. Blistering and ulceration impacting activities of daily living occur in grade 3-4 HFSR. Symptoms typically appear within the first 6 weeks of therapy, often within 1-2 weeks. The cellular defects underlying HFSR likely involve damage to the dermal capillary endothelium, which could increase susceptibility of hand and foot surfaces to mechanical injury and stress after subclinical trauma[28]. Histological examination of lesion palmoplantar skin shows a linear necrotic epidermis with a mild inflammatory infiltrate and vessel ectasia in the dermis[29]. Both sorafenib and sunitinib target stem cell factor receptor (c-Kit) expressed on human keratinocytes, and PDGFR expressed on dermal fibroblasts and endothelial cells, which may impair cell function. HFSR likely results from a combination of capillary damage, inflammation, mechanical stresses, and direct toxicity to keratinocytes and other cell types initiated by targeting of PDGFR, VEGFR, and possibly other receptors[29].

A meta-analysis of 11 clinical studies of sorafenib for RCC and hepatocellular carcinoma showed that sorafenib at the standard dose of 400 mg twice daily increased the risk of HFSR roughly 6.6-fold vs. control, with an incidence of all-grade HFSR of 33.8% (range, 9.1-61.9%)[28]. Both cumulative exposure to sorafenib and the use of combined anti-VEGF therapy appear to exacerbate the incidence and severity HFSR. In a recent study involving 96 patients with advanced solid tumors, cumulative sorafenib exposure correlated with increasing grade of HFSR (P=0.009)[30]. The use of BV with sorafenib was associated with both a higher overall incidence of HFSR (79% compared with 31% with single-agent sorafenib) and a lower cumulative sorafenib dose at which HFSR was observed[30]. Sunitinib is also associated with HFSR, although to a lesser extent than sorafenib[31]. A meta-analysis of 10 clinical studies found an overall HFSR incidence of 18.9% (range, 5.3-38.1%) with sunitinib, which did not differ between intermittent and continuous dosing of this agent[31]. Of interest, the incidence of HFSR in RCC patients is significantly lower with sunitinib than sorafenib (RR, 0.34; P<0.001). Whether this is due to tumor characteristics, targeting of Raf kinase by sorafenib (but not sunitinib), or disparities in patient populations is not clear[31].

Early detection and prompt management of HFSR in patients on sorafenib/sunitnib therapy is essential for minimizing any disruption of therapy, and supportive measures should be started at the first sign of symptoms. A pedicure to remove existing calluses is recommended prior to starting therapy. Patients are advised to wear cotton socks, soft shoes, use gel inserts, and to avoid extremes of temperature and friction on the skin. Moisturizing creams containing urea, salicylic acid, and ammonium lactate can help maintain skin integrity[28, 29]. Pharmacologic agents, including dimethyl sulfoxide (DMSO), oral pyridoxine, systemic steroids, celecoxib, and vitamin E have shown efficacy for treating chemotherapy-associated hand-foot syndrome, but these have not shown utility for HFSR[31]. For patients with grade 2 or 3 HFSR, dose reductions or treatment interruptions may be necessary if symptoms become debilitating. Often, signs and symptoms of HFSR will not recur following dose interruptions[1].

Other dermatologic toxicities

In addition to HFSR, sunitinib and sorafenib are associated with a number of other dermatologic side effects, including rash, skin discoloration, dry skin, alopecia, and hair and nail changes. Skin rash associated with sorafenib closely resembles seborrheic dermatitis, and appears as a homogeneous erythematous and squamous eruption across the mid-facial area and scalp[1]. In a prospective, placebo-controlled study of 85 mRCC patients, facial eruption occurred in 63% of sorafenib-treated patients compared with 2% in the placebo group[32]. Rash typically developed within the first 1-2 weeks of treatment and resolved spontaneously within 2 months. Topical agents with anti-inflammatory properties, including mild topical corticosteroids and antifungal agents have proven beneficial for treating facial rash in an uncontrolled setting. Patients on sorafenib or sunitinib may also develop a papulopustular rash on the face and/or chest and upper back, and rarely, a generalized allergic skin reaction[1]. Other common side effects include painless subungual splinter hemorrhages, mild alopecia (primarily sorafenib), and hair depigmentation (sunitinib)[1]. Sunitinib may also cause yellowing or darkening of the skin, along with focal or diffuse hypopigmentation, often appearing within the first week of treatment and resolving after discontinuation of therapy[1, 33].

In conclusion, antiangiogenic therapies are improving outcomes for many cancer patients, in many cases dramatically. While these therapies are generally well tolerated, they are associated with a variety of distinctive side effects, of which the underlying mechanisms, predisposing risk factors, and true prevalence are not yet fully known. Prospective randomized trials will undoubtedly answer many of these questions. In the meantime, careful monitoring and management of patients on antiangiogenic therapy, utilizing a multi-modality approach and closer collaboration between oncologists and specialists, will help mitigate many of these adverse effects and improve quality of care.

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ACCREDITATION STATEMENT
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RELEASE AND EXPIRATION
Release date is June 30, 2009. Expiration is June 30, 2010.

INTENDED AUDIENCE
Practicing oncologists in the U.S.

EDUCATIONAL OBJECTIVES
At the conclusion of this educational activity, clinicians will be able to:
- Identify the primary side effects of antiangiogenic therapy in patients with cancer.
- Describe the incidence and frequency of side effects of different antiangiogenic agents.
- Discuss strategies for managing of side effects from antiangiogenic therapy and how this may impact patients' treatment and disease course.

METHOD OF PARTICIPATION
Review the illustration and article, then visit www.angio.org and click on CME Publications. There you can register for this CME activity, take the post-test, and access instructions for obtaining CME credits.

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DISCUSSION OF UNLABELLED USE
This CME activity contains discussion of published and/or investigational use of: bevacizumab (Avastin), sorafenib (Nexavar), and sunitinib (Sutent).