Inhibitors of Angiogenesis

New Hopes for Oncologists, New Challenges for Anesthesiologists

Nicolas Libert, M.D.,* Jean-Pierre Tourtier, M.D.,† Lionel Védrine, M.D.,‡ Cyrus Chargari, M.D.§

ANESTHESIOLOGISTS are involved in many aspects of cancer treatment that may interfere with perioperative care. Some of these treatment considerations may have a major impact on patient outcomes.[1,2,3] Basic research in oncology has recently led to a wealth of knowledge about novel biologic pathways for more efficient and selective tumor cell targeting. Antiangiogenic therapy has demonstrated significant activity in patients with solid tumors, such as metastatic breast cancer, renal cell carcinoma, brain tumors, non-small-cell lung cancers, and colorectal carcinoma (table 1). By targeting vascular endothelial growth factor (VEGF), these agents have demonstrated clinical efficacy in medical oncology. However, angiogenic factors are also involved in a number of physiologic processes, including tissue remodeling and wound repair. The VEGF family consists of seven related glycoproteins (VEGF-A, B, C, D, E, and placenta growth factors 1 and 2). Commonly referred to as VEGF, VEGF-A was initially identified by its ability to increase vascular permeability. The most important effects of VEGF include endothelial cell activation, tumor growth, and cell migration.[4] The physiologic function of VEGF is to generate new blood vessels after injury to promote collateral circulation. Its production is induced in hypoxic cells through hypoxia-inducible factor (HIF) production. Circulating VEGF then binds to VEGF receptors on endothelial cells, leading to angiogenesis.

Two main anti-VEGF strategies have been developed over recent years: neutralizing anti-VEGF antibody and small molecule tyrosine kinase inhibitors (TKI) targeted against VEGF receptors. While potentially improving overall survival, inhibitors of VEGF are subject to considerable uncertainty concerning their potential toxicity. An increase in wound complications and thromboembolic events has been observed in patients who undergo surgery while receiving inhibitors of angiogenesis. This paper highlights the toxicities of VEGF inhibitors, with special focus on consequences for anesthesiologists.

Bevacizumab

Biologic Highlights

Bevacizumab is a humanized monoclonal antibody directed against all isoforms of VEGF. It directly binds to VEGF, thus preventing its ability to interact with its cellular receptors (VEGF receptors). It has demonstrated promising activity against many primary tumors. Several mechanisms of action for bevacizumab have been proposed. The most important seem to be direct antiangiogenic activity effects and normalization of tumor blood vasculature. Due to anarchic neoangiogenesis, tumoral vasculature is characterized by tortuous and leaky vessels. Consequently, VEGF is overexpressed in most tumor cells in response to chronic hypoxia. Bevacizumab blocks survival signaling pathways in endothelial cells within tumor vasculature. By decreasing the number of abnormal tumor-associated microvessels (reduced angiogenesis), bevacizumab deprives the tumor of nutrients. Bevacizumab also normalizes the tumor vasculature: it decreases vascular permeability and interstitial fluid pressure in the tumor. Consequently, it allows for better delivery of cytotoxic agents and partially alleviates hypoxia, which is an important factor of tumor resistance toward chemotherapy or radiotherapy. Rationally, targeting the VEGF has shown promising preclinical and clinical anticancer activity. However, several concerns have been raised regarding a possible increased risk for hemorrhages, cardiovascular events, and thromboembolic events (table 2). The estimated half-life of bevacizumab is approximately 20 days (table 1),[5] but the effects of bevacizumab may lead to long-lasting changes in the vascular physiology.

* Resident, Department of Anesthesia and Critical Care, † Senior Anesthesiologist, Department of Anesthesia and Critical Care, ‡ Professor, § Resident, Unit of Medical and Radiation Oncology, Hôpital d'instruction des armées du Val de Grâce, Paris, France.

Address correspondence to Dr. Libert: Département d'anesthésie réanimation, Hôpital d'instruction des armées du Val de Grâce, 74 Bd de Port Royal, 75005 Paris, France. nicolaslibert@free.fr. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Table 1. Indications, Pharmacokinetics, and Implications of Angiogenesis Inhibitors for the Perioperative Period

	Bevacizumab	TKI
Indications	Glioblastoma, metastatic colorectal cancer, metastatic breast cancer, advanced or metastatic NSCLC, advanced or metastatic RCC	• Sunitinib: gastrointestinal stromal tumor, RCC • Sorafenib: hepatocellular carcinoma, RCC
Half life	20 days (range: from 11 to 50 days)	• Sunitinib: 40 to 60 h • Sorafenib: 25 to 48 h
Elimination	Metabolized and eliminated *via* the reticuloendothelial system	Hepatic metabolism Elimination: mainly fecal (61-77%) and renal (16-19%)
Drug interactions	No drug interaction reported. No significant increase in severe bleeding events among patients treated with low dose aspirin.	Concentrations may be: • Decreased by inducers of the CYP3A4 • Increased by inhibitors of the CYP3A4
Delay between treatment and surgery	Major surgery: 6 to 8 weeks* Minor surgery: 28 days	Insufficient data to conclude One week recommended empirically
Preoperative evaluation	EKG (QT prolongation), ± echocardiography, renal function, coagulation testing, blood count, ionogram, albuminemia†, thyroid stimulating hormone (TKI)	

* Less data are available for diseases other than colorectal cancer.   † If ≤2+ on dipstick.
EKG = electrocardiogram; NSCLC = nonsmall-cell lung cancer; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitors.

The apparent disparate association of both bleeding and thromboembolic events may be explained by susceptibility of tumor-associated new blood vessels to both increased permeability and thrombosis, particularly in the circumstance of endothelial cells perturbed by the VEGF targeting. Life threatening hemorrhages are related to massive tumor necrosis and decreased replenishment ability of endothelial cells within tumor neovessels.[6] Bevacizumab decreases renewal of endothelial cells, with a risk of acute bleeding. Inhibition of the indirect procoagulant activities of VEGF may favor hemorrhagic risk. VEGF is also an essential protection factor for endothelium, with multiple biologic functions, including the production of vasoactive mediators and hemostatic components. Consequently, blocking VEGF may lead to endothelial dysfunction and cause adverse vascular effects, such as venous and arterial thromboembolic events.[7] Several other mechanisms have been advocated for the thrombotic effect of bevacizumab: subendothelial activating procoagulant phospholipids exposure, decrease in nitric oxide and prostaglandin, overproduction of erythropoietin, or expression of inflammatory cytokines causing *in situ* thrombus formation. Up to 30% of patients receiving bevacizumab develop treatment-related hypertension. This is related to a decreased production of endothelial nitric oxide, which is a strong vasodilatator, leading to increased platelet aggregation and adhesion to the vascular endothelium. The reduction in the density of microvascular beds has also been proposed as another possible mechanism. Moreover, the cytotoxic effect of bevacizumab releases procoagulant from the tumor into the blood circulation. Another important point regarding the bev-

acizumab-related cardiovascular adverse effects is that the VEGF probably plays a key role in the development of collateral vessels in patients with coronary insufficiency. Inhibiting the VEGF might contribute to decompensation of a subjacent coronary obstructive disease.

Clinical Assessment

Adverse cardiovascular events were reported in pivotal studies, including fatal hemorrhages and arterial thromboses (table 2). These toxicities emerged as frequent and were observed in about 10% of patients receiving bevacizumab in combination with chemotherapy.[8] In phase III studies, data regarding the bleeding risk are more controversial. Escudier *et al.* reported in patients with renal cell carcinoma that all grade bleeding events were higher in the bevacizumab group, with 112/337 (33%) *versus* 28/304 (9%) in the control group, but this difference was attenuated regarding severe bleeding events: 11/337 (3%) *versus* 1/304 (less than 1%).[9] No significant increase was reported in patients with metastatic colorectal carcinoma.[10]

Most bleeding observed with bevacizumab is mild spontaneous mucocutaneous bleeding. Epistaxis is observed in about 20 to 40% of patients. However, severe life-threatening hemoptysis and pulmonary bleeding were reported in the experimental arm of a trial with squamous cell lung cancer patients receiving carboplatin and paclitaxel with or without bevacizumab. Pulmonary bleeding is probably tumor-site related, and the histologic type is of first importance when assessing the risk for severe bleeding, particularly in patients with proximal squamous cell lung cancer.

Table 2. Major Adverse Effects of Angiogenesis and Their Frequencies

	Bevacizumab	TKI
Mild/Moderate bleeding	Up to 30% of patients	Up to 20%, mainly low grade epistaxis
Severe bleeding	Rare: <5%	Rare: <5%
Arterial thrombosis	Rare: 4%	Thromboembolic events rarely reported
Venous thrombosis	Up to 19%	
Cardiac toxicity	Left ventricular dysfunction: • All grade <15% • Grade 3 and 4 < 1%	Left ventricular dysfunction: • All grade <15% • Grade 3 and 4 < 3% Cardiac ischemia: up to 5%
Mild/Moderate hypertension	Up to 30%	15-25%
Severe hypertension	10-15%	5-15%
Kidney injury	Proteinuria up to 40% with RCC	Creatinine increase up to 65% in RCC, less in other indications
Neutropenia, thrombopenia, or anemia	All grade up to 37%	All grade up to 72%
Hypothyroidism	Rare: <1%	Up to 85% for sunitinib Up to 18% for sorafenib
Wound healing	Rare: 2%, increased risk of gastrointestinal perforation, bowel perforation, and anastomotic leak	No evidence of increase in perioperative complications
Other toxicities	Infection grade 3-4 up to 9%	Diarrhea up to 40%

Adverse effects depend on associated chemotherapy.
RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitors (sunitinib and sorafenib).

A pooled analysis of five randomized controlled trials assessed the risk of an arterial or venous thromboembolic event in patients treated with chemotherapy and bevacizumab.[11] Although the overall rate of venous thrombosis in this study was approximately 10%, bevacizumab was not associated with an increased risk for venous thromboembolic events (hazard ratio = 0.89; 95% CI, 0.66–1.20; $P = 0.44$). However, it was demonstrated that combined treatment with bevacizumab and chemotherapy was associated with an increased risk for an arterial thromboembolic events, when compared with chemotherapy alone (hazard ratio = 2.0; 95% CI, 1.05–3.75; $P = 0.031$). An arterial thrombosis that resulted in death within 30 days of onset was documented in 0.62% (95% CI, 0.29% to 1.35%) of bevacizumab-treated patients *versus* in 0.26% (95% CI, 0.08–0.9) of control patients. Most arterial thromboembolic events were coronary or cerebrovascular events. Development of a bevacizumab-related arterial thrombosis was associated with a prior arterial thromboembolic event ($P < 0.001$) or age of 65 yr or older ($P = 0.01$). The authors found no significant increase in risk for a bleeding event between aspirin users and nonusers among bevacizumab-treated patients. In a recent meta-analysis

from 15 randomized controlled trials including 7,956 patients with advanced solid tumors, it was suggested that the incidence of venous thromboembolism in patients with advanced cancer would increase by about 33% during treatment with bevacizumab. Interestingly, this risk was similarly increased for bevacizumab at two different schedules (2.5 or 5 mg/kg *per* week). The highest incidence was observed among patients with colorectal cancer; meta-analysis showed that the incidence of all-grade venous thromboembolism was 19.1%. It is important to note that the relative risk of high-grade venous thromboembolism with bevacizumab was shown to vary with tumor type, ranging from 1.00 (95% CI, 0.58–1.72) in pancreatic cancer to 2.86 (95% CI, 0.62–13.24) in renal cell carcinoma.[7]

These results suggest a modest increase in the risk of arterial thromboembolic events among patients treated with bevacizumab. However, this risk is significantly increased among patients with a reported history of a cardiovascular event or who were more than 65 yr old. No strong conclusion could be drawn from these results about the benefit of aspirin-based prophylaxis, which should be considered for patients who are at high risk for an arterial thromboembolic event.

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In a large phase III trial of 813 patients, combining bevacizumab (5 mg per kilogram) with irinotecan, fluorouracil, and leucovorin improved survival compared with chemotherapy alone for metastatic colorectal carcinoma.[10] Although easily managed with standard antihypertensive agents, grade 3 hypertension was more common in the group with bevacizumab (11.0% *vs.* 2.3%). Hypertension was the only significantly increased side effect. It was suggested that bevacizumab-related hypertension would be dose-dependent. Its extent might reflect the level of target inhibition. In the combined analysis by Kabbinavar *et al.*, 16% of patients receiving bevacizumab developed high grade hypertension, *versus* 3% of the control arm. Most patients had a history of hypertension. One patient discontinued bevacizumab because of angina and hypertension.[8] Severe hypertensive crises have also been reported.[12] Mild and asymptomatic proteinuria is frequent, but grade 3 proteinuria may occur in up to 3% of patients whatever their primary tumors, and up to 8% with renal cell carcinoma.[9] The renal toxicity of bevacizumab (thrombotic microangiopathy) is due to a reduction in glomerular VEGF.[13] Proteinuria may progress to nephrotic syndrome and renal failure. Consequently, all patients receiving bevacizumab should be monitored for proteinuria and creatinine. This suggests that great consideration should be given regarding renal function in patients receiving bevacizumab.

A systematic meta-analysis of published randomized controlled trials assessed the risk of bevacizumab-related gastrointestinal perforation in 12,294 patients with various solid tumors.[14] It found an overall incidence of 0.9%. Although this incidence was low, the addition of bevacizumab to conventional chemotherapy significantly increased the risk of gastrointestinal perforation, with a relative risk of 2.14 (95% CI, 1.19–3.85), which was increased with higher doses: 2.67 (95% CI, 1.14–6.26) and 1.61 (95% CI, 0.76–3.38) at 5 and 2.5 mg/kg per week, respectively. Higher risks were observed in patients with colorectal carcinoma (relative risk: 3.1; 95% CI, 1.26–7.63) and renal cell carcinoma (relative risk: 5.67; 95% CI, 0.66–48.42). In a retrospective analysis of 1,442 patients with various malignancies treated with bevacizumab, Badgwell *et al.* reported bowel perforation in 24 patients (1.7%).[15] Seven patients underwent percutaneous catheter placement for drainage. Only five patients underwent surgery, and another patient developed a subsequent anastomotic leak. The remaining patients were treated with antibiotics only. It is of note that local risk factors for perforation were found in most patients. In four patients, the bowel perforation developed at the site of a previous surgical anastomosis. The median time to perforation after initiation of bevacizumab treatment was 71 days (range 3–512 days). The overall 60-day mortality rate was 25%; however, no death during this period was related to the perforation. Finally, an increased risk of bowel perforation has been reported after treatment with bevacizumab in patients with metastatic ovarian cancer.[14] Due to more extensive mesenteric tumor infiltration, patients with advanced disease would be at particularly high risk.

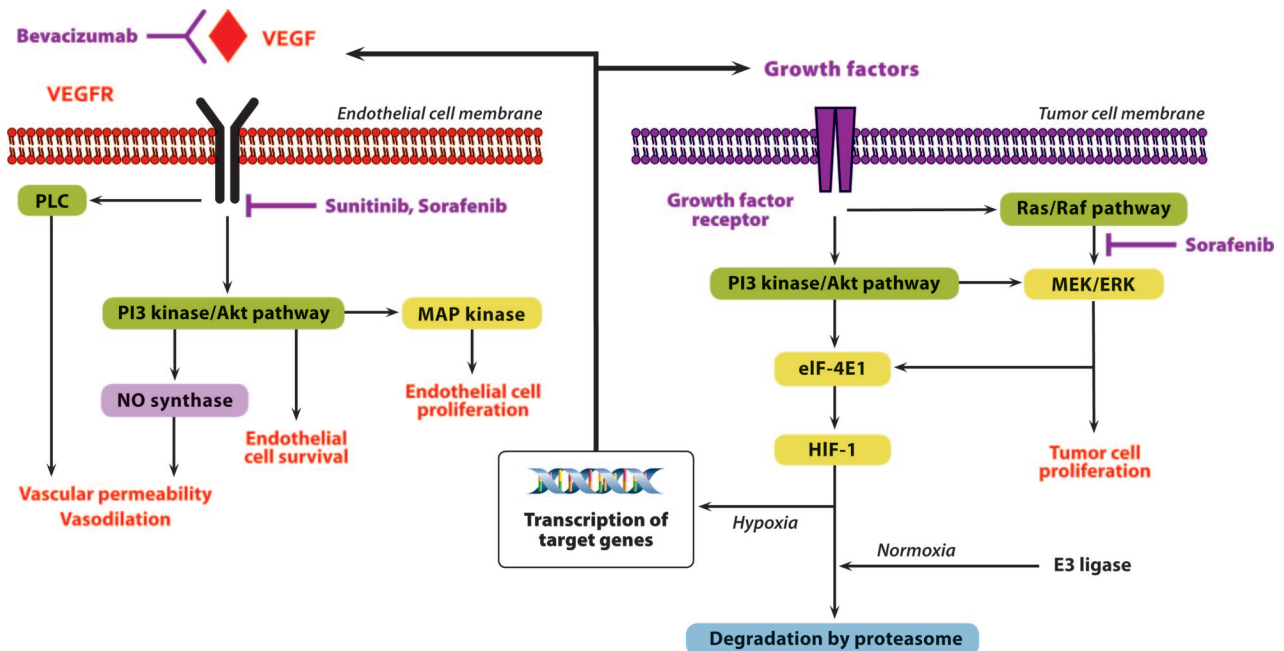## Tyrosine Kinase Inhibitors

Biologic Highlights

Sunitinib malate and sorafenib are oral inhibitors of several growth factor receptors, including the VEGF receptor, the platelet-derived growth factor receptor, and the stem cell factor. The antiangiogenic and antitumor activities of sunitinib are attributable to the inhibition of phosphorylation of several tyrosine kinase receptors, including receptors for platelet-derived growth factor, VEGF receptor, and stem cell factor receptors (fig. 1). The half-life of sunitinib is approximately 40 to 60 h (table 1). Significant clinical benefit of sunitinib has been demonstrated in patients with metastatic renal cell carcinoma.[16] Moreover, sunitinib is effective as second line therapy in the treatment of advanced gastrointestinal stromal tumors. Sorafenib has inhibitor activity against Raf kinase and several tyrosine kinase receptors, including VEGF receptor 2, platelet-derived growth factor, Fms-like tyrosine kinase 3, Ret, and c-Kit. The antitumor activity of sorafenib may be attributed to inhibition of tumor angiogenesis and direct effects on tumor cell proliferation/survival. The mean half-life of sorafenib is approximately 25 to 48 h. By targeting HIF-1 gene pathways, both agents have also shown strong antiangiogenic and antitumor activity as single-agent therapies in renal cell carcinoma.[17] HIF-1–related gene products are physiologic mediators of myocardial remodeling, acute and chronic ischemia, and vascular permeability. Moreover, the HIF transcriptional complex mediates the cellular response to hypoxic stress, resulting in the transcription of the VEGF, platelet-derived growth factor, transforming growth factor β, and erythropoietin (fig. 1). Although sunitinib and sorafenib are usually well-tolerated, significant toxicities were reported.

Clinical Assessment

Few vascular toxicities or cardiovascular events have been reported with sunitinib and sorafenib (table 2). A slight increase of bleeding complications has been reported in clinical assessments, mainly grade I and II epistaxis.[16,18] No evidence of a systematic decrease in left ventricular ejection fraction (LVEF) could be found in 312 patients with unresectable gastrointestinal stromal tumor receiving either sunitinib or placebo.[18] However, high grade treatment-related hypertension was reported in 3% of sunitinib-treated patients. Motzer *et al.* prospectively demonstrated that sunitinib improved overall survival compared with interferon α first-line treatment of patients with metastatic renal cell carcinoma.[16] The treatment-related adverse event of LVEF decline was reported in 50 patients (13%) in the sunitinib group compared with 12 patients (3%) in the interferon α group, including grade 3 toxicities in 10 patients (3%) and three patients (1%), respectively. The comparison between the sunitinib group and the interferon α group was significant for severe hypertension (13% *vs.* 3%, $P < 0.05$).

A recent systematic review by Zhu *et al.* focused on the incidence of hypertension in patients receiving sunitinib for a metastatic renal cell carcinoma or a gastrointestinal stromal tumor. A total of 4,999 patients from 13 clinical trials were

Fig. 1. Mechanisms of action for bevacizumab and tyrosine kinase inhibitors. VEGF is a ligand for one of the three structurally similar tyrosine kinase receptors, which are VEGFR-1 (also known as FLT1), VEGFR-2 (also known as KDR), and VEGFR-3 (also known as FLT4). Binding of VEGF results in multiple signaling networks activation. VEGFR-1 is able to bind to VEGF-A, VEGF-B, and PlGF. VEGFR-2 is activated by VEGF-A, VEGF-C, and VEGF-D, while VEGF-R3 is activated by VEGF-C and VEGF-D. Monoclonal antibody bevacizumab is highly specific for VEGF-A and targets the VEGF on the endothelial cell membrane. Sunitinib and sorafenib target the transmembranar tyrosine kinase receptor. Activation of PI3kinase and MAPkinase pathways is involved in the angiogenesis process. Sorafenib also inhibits the Ras/Raf pathways, which plays a major role in tumor cell proliferation. Akt = serine/threonine protein kinase Akt, also known as protein kinase B; elf–4E1 = eukaryotic initiating factor –4E1; E3 ligase = ubiquitin E3 ligase; HIF = hypoxia inductible factor; MAP kinase = mitogen activated protein kinase; MEK/ERK = mitogen-activated protein kinase/ extracellular signal-regulated kinase; NO synthase = nitric oxide synthase; PI3 kinase = phosphatidyl-inositol 3-kinase; PLC = phospholipase C; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

included for analysis.[19] Among patients receiving sunitinib, the incidence of all-grade and high-grade hypertensions was 21.6% (95% CI, 18.7–24.8) and 6.8% (95% CI, 5.3–8.8), respectively. The authors found that sunitinib was associated with a significantly increased risk of high-grade hypertension (relative risk: 22.72; 95% CI, 4.48–115.29, $P < 0.001$) and renal dysfunction (relative risk: 1.36; 95% CI, 1.20–1.54, $P < 0.001$). The mechanisms of hypertension associated with TKI may be partially related to their antagonistic effect on VEGF signal pathways, which results in endothelial dysfunction with reduced nitric oxide production. Other mechanisms include vascular rarefaction and increased arterial stiffness.[20,21] Khakoo *et al.* retrospectively reported that patients treated with sunitinib may develop left ventricular dysfunction, most of which were not completely reversible.[22] It was hypothesized that heart failure after TKI treatment could be partially due to direct cardiomyocyte toxicity and exacerbated by hypertension. Preclinical assessments showed that TKI may induce apoptosis in cardiomyocytes. The cardiac effects of VEGF are not limited to blood vessel formation and depend on the type of VEGF. Expression of VEGF-A and B seems to be important in cases of cardiac hypertrophy or after infarction; they prevent apoptosis and maintain contractile function. In animal models of cardiac dysfunction, while VEGF-B in the heart induced only a modest angiogenic response compared to VEGF-A, its transduction in the heart modified the gene expression profile, resulting in preserving LVEF function after myocardial infarction. Because VEGF inhibitors act differently on VEGF subtypes, this could explain the different side effects of the different drugs. In patients with renal cell carcinoma, the use of sunitinib has been associated with cardiac ischemia in 3% and with a decline of the LVEF in 10%.[23] When analyzing the toxicity of sunitinib or sorafenib treatment for renal cell carcinoma, it was found that 33.8% of patients experienced a cardiac event, and 40.5% had electrocardiographic changes. About 10% were seriously compromised, although all of them recovered after cardiovascular management.[17] It is important to note that sunitinib may induce prolongation in the QT interval, resulting in an increased risk of ventricular arrhythmias.

Since more than 90% of patients with renal cell carcinoma treated with sunitinib had a prior nephrectomy, the risk of hypertension may be also increased by renal dysfunction from sunitinib. This suggests that renal function should be monitored closely, especially in renal cell carcinoma patients who already have reduced glomerular filtration rates. The risk of hypertension related to TKI is higher in patients with renal cell carcinoma compared to other indications. Interestingly, compared to bevacizumab, proteinurias are rarely reported with TKI, but

these events may be underestimated.[24] Renal thrombotic microangiopathies have also been described.

Antiangiogenesis therapy using TKI has also been associated with severe bleeding. In a phase II study, Socinski *et al.* evaluated the clinical activity and tolerability of 50 mg/day of sunitinib in 63 patients with previously treated, advanced non-small-cell lung cancers carcinoma.[25] Three cases of fatal bleeding occurred, two of which were considered drug related.

Few thromboembolic events were observed with sorafenib. Escudier *et al.* prospectively reported on 903 patients treated either with placebo or with sorafenib as second line for a renal cell carcinoma.[26] Arterial complications occurred significantly more frequently in the sorafenib group than in the placebo group. Those complications included cardiac ischemia in 22 patients (4.9%), with 6 events reported as related to the study drug. The sorafenib group had a longer follow-up time. Central nervous system ischemia was reported by seven sorafenib patients (1.5%), compared with three patients (0.7%) in the placebo group. The rate of severe hemorrhages was comparable in both groups and only low grade bleeding events were more frequent in the sorafenib group.

Finally, TKI may lead to myelotoxicity.[16] This has been more rarely observed with bevacizumab monotherapy. These toxicities seem to be less frequent with sorafenib.

Angiogenesis Inhibitors and Perioperative Complications

Implications for surgery and perioperative wound complications have recently been reviewed.[27] Few prospective data have specifically assessed the risk for perioperative complications in patients receiving angiogenesis inhibitors. Although the integration of targeted therapy and surgery requires careful consideration due to the potential for increased perioperative morbidity, preliminary data suggest that the use of targeted therapies before nephrectomy would not significantly increase the risk for perioperative complications. Two different situations should be identified: surgery in patients previously treated with VEGF inhibitors, and those patients who underwent emergency surgery while still receiving treatment. Recently, Thomas *et al.* reported that surgical resection of renal cell carcinoma after targeted therapy was feasible, with low morbidity in most patients.[28] The authors retrospectively identified 19 patients with renal cell carcinoma treated with sunitinib, sorafenib, or bevacizumab plus interleukin-2 before surgical extirpation. Perioperative complications were noted in 16% of patients. One patient had a significant intraoperative hemorrhage and disseminated intravascular coagulopathy from a concomitant liver resection. An anastomotic bowel leak and abscess were observed postoperatively in another patient. Minor wound complications were reported in two patients. Results from a recent phase II trial suggested that neoadjuvant bevacizumab therapy would yield clinical outcomes comparable to postsurgical treatment with antiangiogenic therapy in patients with metastatic renal cell carcinoma.[29] In this trial, 52 patients received bevacizumab plus erlotinib (n = 23) or bevacizumab alone (n = 27) for 8 weeks, then 42 patients underwent nephrectomy. Two perioperative deaths occurred, but these were not drug related. However, wound dehiscence resulted in treatment disruption for five patients. Margulis *et al.* retrospectively assessed perioperative complications in patients treated with inhibitors of angiogenesis before nephrectomy or resection of retroperitoneal renal cell carcinoma recurrence, and compared them to a matched patient cohort who underwent up-front surgery.[30] Median delay from therapy to surgery was 40, 11, and 20 days in patients with bevacizumab (n = 17), sunitinib (n = 12), and sorafenib (n = 15), respectively. The authors found no significant differences in surgical parameters; incidence of perioperative mortality; reexploration; thromboembolic events; cardiovascular, pulmonary, or gastrointestinal complications; or infections between the two groups. Procedural difficulty was not significantly affected. However, significant heterogeneity in types of preoperative therapy or interval from last administration to nephrectomy diminished the power of this analysis.

Perioperative angiogenesis inhibitors are now commonly used in patients undergoing hepatic resection. Recently, results from a phase II trial suggested that bevacizumab could be safely administered until 5 weeks before liver resection in patients with metastatic colorectal carcinoma without increasing the rate of surgical complications or severity of bleeding.[31] The authors reported on 56 patients with colorectal carcinoma with liver metastases potentially curable by liver resection. The patients received biweekly bevacizumab plus capecitabine and oxaliplatin for 6 cycles, then underwent liver resection, including 11 patients with synchronous primary tumor resection. It should be noted that bevacizumab was excluded from the sixth cycle of therapy; thus the delay between the last administration of bevacizumab and surgery was 5 weeks. No increased bleeding or wound-healing complications were observed and only three patients (6%) required perioperative blood transfusions. No postoperative mortality occurred, and morbidity was observed in 11 patients (20%). D'Angelica *et al.* reported no significant difference in perioperative morbidity for 32 patients who had undergone hepatectomy for colorectal metastases, although they had received bevacizumab within 12 weeks of surgery.[32] Perioperative complications were encountered in 13 patients (41%), which was similar to what had been observed in a set of matched controls. Sixteen and 24 patients had received bevacizumab before and/or after hepatectomy, respectively. The median time between last bevacizumab administration and surgery was 6.9 weeks before (range 3–15) and 7.4 weeks after (range 5–15). Reddy *et al.* also retrospectively found no significant increase in perioperative complications in patients receiving bevacizumab and chemotherapy compared with chemotherapy alone, but suggested a trend toward fewer complications if the bevacizumab was held for more than 8 weeks before hepatic resection.[33] When urgent surgery is required, the time frame for stopping angiogenesis inhibitors is beyond the physician's control. Scappaticci *et al.* compared

wound healing complications in the situation of major surgery during treatment with bevacizumab. It was found that 13% patients treated with bevacizumab experienced wound healing complications, *versus* 3.4% of control patients.[34]

The appropriate interval between bevacizumab and subsequent elective surgery remains debated. A window of 6 to 8 weeks may be reasonably recommended. After minor surgery, bevacizumab does not seem to significantly affect wound healing. However, it seems reasonable that postoperative reintroduction of bevacizumab should wait $\geq$ 28 days to prevent wound healing complications (table 1). After major surgery, randomized studies showed an increase in wound-healing complications in patients who had received bevacizumab therapy, suggesting a need to withhold bevacizumab for at least 40–60 days. It appears that TKI do not drastically increase the risk for thromboses. However, high-grade hypertensions were more frequent, and fatal bleeding may potentially occur. We believe that cardiac damage from TKI has probably been underestimated, and the preoperative evaluation should be careful. Clinical evidences suggest that arterial blood pressure and LVEF should be closely monitored in patients with cardiac risk factors who are treated with a TKI. For patients without cardiac risk factors, a baseline evaluation of the LVEF should be considered. We recommend caution in patients with a history of QT prolongation and in those taking antiarrhythmics, or patients with electrolyte disturbances. No data are available for patients treated with antiplatelet therapy during the perioperative period; because the risk of hemorrhage could be increased this is probably an important issue.

Drug Interactions

Drug interactions are of particular importance owing to the narrow therapeutic ratio and potential toxicities of angiogenesis inhibitors. Clinical data are limited, but preclinical results suggest that anesthetic drugs may potentially decrease the efficacy of angiogenesis inhibitors. Moreover, targeted therapies may potentially modify the response to anesthetic drugs, including hypnotics and analgesics. No strong drug interaction has been evidenced for bevacizumab but the metabolism of TKI is affected by modulators of the CYP3A4 family (table 1).

As previously stated, the HIF-1 transcriptional complex mediates the cellular response to a hypoxic environment, resulting in VEGF and PDGF activation. TKI contribute to suppression of levels of HIF-1, leading to cell death. Burkitt *et al.* demonstrated that tumor angiogenesis and perfusion were almost completely inhibited by sunitinib when both HIF-1α and HIF-2α genes were disrupted.[35] Since the HIF-1 level predicts sensitivity to sunitinib, drugs that affect the expression of HIF-1 gene pathways may theoretically modulate the activity and/or toxicity of TKI. Interestingly, anesthetic drugs have been reported to affect HIF-1 activity. In recent years, evidence has demonstrated that the activation of PI3K-Akt prosurvival kinase cascade signaling pathways was a key phenomenon in volatile anesthetics-induced cardiac and cerebral preconditioning and postconditioning properties. It has also been demonstrated for isoflurane

and for xenon that their cellular protective effects were linked to hyperexpression of HIF-1α and that they activate its downstream effectors like erythropoietin and VEGF in a time-dependent manner.[36–38] In contrast, halothane and barbiturates block HIF-1 activity and downstream target gene expressions.[39] Whether volatile-anesthetics keep their preconditioning and postconditioning effects under TKI is unknown. Takabuchi *et al.* investigated the effect of opioids on HIF-1 activity. They showed that the opioid receptor-mediated signals do not significantly affect HIF-1-dependent gene responses.[40] However, Roy *et al.* have demonstrated that morphine inhibits phosphorylation of HIF-1α and cardiac myocyte VEGF synthesis.[41]

As highlighted by Izzedine *et al.*, no strong recommendation could be made for the management of hypertension related to VEGF inhibitors. In most patients, hypertension could be treated with standard medications.[42] However, nondihydropyridine calcium blockers verapamil and diltiazem are CYP3A4 inhibitors and should not be used in combination with sunitinib or sorafenib. Nifedipine may induce VEGF secretion. Dihydropyridine calcium channel blockers such as amlodipine and felodipine might be recommended, but should be individualized to the clinical circumstances. Drugs increasing the nitric oxide level, such as nitrates or phosphodiesterase inhibitors, have been successfully used as antihypertensive therapy. However, only short-term treatment should be considered, because increasing the nitric oxide level may induce a proangiogenic activity. To our knowledge, there is also no clinical evidence of a strong interaction between diuretics and angiogenesis inhibitors.

Conclusions and Perspectives

Cautious attention to the cardiovascular and hemostatic adverse effect profile of these antiangiogenic therapies is crucial during their use in clinical routines, particularly in patients at high risk for cardiovascular events who may have received anthracyclin or heart irradiation. Although cardiovascular events have been frequently reported in patients treated with bevacizumab or TKI, preliminary experiences suggest that surgical resection can be performed safely after systemic therapy with VEGF inhibitors, without significant increase in perioperative morbidity or mortality. However, appraisal of tomorrow's treatments implicates new risks for anesthesia, justifying the design of a more comprehensive and multidisciplinary approach when assessing the risks for cardiovascular complications. Due to the lack of prospective clinical data, strong recommendations cannot be given. Given the interplay pathways between angiogenesis and the blood clotting system, a better understanding of the impact of angiogenesis inhibitors on hemostatic balance is required. Analysis of adverse events from ongoing clinical trials should help to further predict the anesthetic risk. Prospective registration of perioperative cardiovascular events would be a first simple step toward improved definition of high-risk patients and toward strong recommendations. Finally, interferences of these drugs with pain management have not been thoroughly investigated, and recent data regarding chemotherapy encourage further assessment in this setting.[43]

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■ ANESTHESIOLOGY REFLECTIONS

The 45-cent Harvey Cushing Stamp

Anesthesiologists hail Harvey Cushing, M.D. (1869–1939), for popularizing intraoperative anesthetic records, sphygmomanometry, and precordial auscultation. Himself a world-class illustrator as well as neurosurgeon, Cushing was portrayed with charcoal by John Singer Sargent in 1916, a full 72 yr before the 1988 first-day issue of that portrait on a 45-cent stamp by the U.S. Postal Service. That release frustrated efforts to honor dentist-anesthetist Horace Wells but certainly pleased U.S. President Ronald Reagan, who had unveiled the stamp on Cushing's birthday in 1987 at the White House Rose Garden before the adopted daughter of Cushing's neurosurgical disciple Loyal Davis—First Lady Nancy Davis Reagan. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Libert *et al.*