Thromboprophylaxis in Cancer Patients Receiving Bevacizumab

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BACKGROUND: Thrombosis is one of the leading causes of death in cancer patients. Anti-angiogenic inhibitors like bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor, increase the risk of thrombosis. Thromboprophylaxis must be provided to patients receiving bevacizumab.

METHODS: An up-to-date, comprehensive literature search using PubMed for studies performed on bevacizumab from January 2003 to the present was performed. Key words searched included bevacizumab, avastin, thromboprophylaxis, and anticoagulation in cancer patients.

RESULTS: Thrombosis risk is increased with bevacizumab therapy. Anticoagulation therapy with bevacizumab may increase bleeding risks; however, these risks are generally low and for minor bleeding. Current guidelines approve thromboprophylaxis in a subset of cancer patients; however, they are not specific for patients receiving anti-angiogenesis therapy.

CONCLUSION: Thromboprophylaxis should be considered for patients receiving bevacizumab, as the benefits outweigh the small risk of adverse effects such as bleeding.

KEYWORDS: Angiogenesis inhibition, bevacizumab, avastin, chemotherapy, thromboprophylaxis, anticoagulation, cancer patients

The incidence of thrombosis continues to increase in populations of patients with cancer, in which it is the second most common cause of death.[1] Owing to the nature of their conditions, cancer patients are at especially high risk of developing thrombotic complications, a risk that can be further exacerbated by treatment regimens such as chemotherapy, surgery, and anti-angiogenic therapy.

Tumor cells require a blood supply to receive nutrients and oxygen, a need met by a process called angiogenesis, in which tumor cells release a large protein, vascular endothelial growth factor (VEGF). Angiogenesis occurs in cancer patients when VEGF binds to receptors on nearby blood vessels, which helps initiate the growth of new blood vessels, ultimately feeding the tumor.[2] Angiogenesis becomes uncontrolled during cancer development owing to the continuous release of VEGF. Consequently, cancer patients have high serum levels of VEGF.[3] Angiogenesis is also a means of tumor metastasis to other parts of the body. Blocking VEGF from binding to its receptors, therefore, prevents the growth of tumor cells, and VEGF inhibition has become a key goal in cancer therapy.

Bevacizumab, a recombinant humanized monoclonal antibody against VEGF that has been approved for the treatment of many advanced solid tumors, is associated with fatal thrombotic complications. Owing to the high prevalence of thrombosis in cancer patients receiving bevacizumab, prophylactic treatment to prevent the morbidity and mortality associated with thrombosis in oncology patients is critical. Therefore, it is necessary to assess both the benefits and the risks of thromboprophylactic therapy in patients treated with bevacizumab. This review summarizes studies of thromboembolic events associated with bevacizumab and discusses the current guidelines for thromboprophylaxis in cancer patients.

Thrombosis in Cancer

Cancer patients are predisposed to a hypercoagulable state owing to the nature of their condition, which imparts a 4-fold increased risk of thrombosis, the second-leading cause of death in these patients.[4-6] The association between cancer and thrombosis works circularly, with cancer inducing a hypercoagulable state and the pro-thrombotic changes in turn facilitating cancer growth and metastasis.[6] A complex interaction

of numerous pathways perpetuates the disease state, which can be explained by 3 key factors that trigger thrombosis through Virchow's triad: endothelial damage, hemodynamic instability, and hypercoagulation.[3] Each component is evidently expressed in cancer patients.

The endothelium plays a critical role in thrombosis. The endothelium maintains the balance of the intravascular anti-thrombotic state; however, cancer cells can transform the endothelium to a pro-thrombotic surface through inflammatory stimuli by the secretion of cytokines and growth factors.[7] In addition, increased blood viscosity, mechanical blockage through tumor external compression or invasion, or patient immobility can precipitate hemodynamic instability and thus enhance the likelihood of clot formation. Finally, hyper-coagulation is stemmed through the imbalance of pro- and anticoagulation, an increase in overall platelet activity, and a decrease in fibrinolytic activity.[8]

The release of pro-coagulants from tumor cells such as tissue factor (TF) and thrombin (IIa) creates a more complex issue in cancer patients owing to the disproportion in the pro-coagulant and anticoagulant states. TF has many roles in the hemostatic system: it is the principal initiator of the clotting cascade, regulates the expression of VEGF, and promotes angiogenesis with thrombin.[7] Venous thromboembolism (VTE) occurs more frequently among patients with higher levels of TF expression and leads to a poorer prognosis in those with ovarian and pancreatic cancers.[9] Conversely, thrombin may increase platelet adhesion to tumor cells, further enhancing tumor progression.[3,7] As a result, thrombosis further increases mortality in cancer patients; therefore, physicians and patients alike must be hyper-vigilant for thrombosis after a diagnosis of cancer.

VEGF Inhibitors/Anti-Angiogenic Agents

Many mechanisms of tumor invasion and angiogenesis overlap in the pathophysiology of cancer-related thrombosis.[10] VEGF inhibitors and anti-angiogenesis agents have been developed as innovative therapies to reduce cancer metastasis but are themselves associated with particularly high rates of thrombosis. Both VTE and arterial thromboembolism (ATE) have been linked to anti-angiogenic therapy. Normally, VEGF maintains endothelial function; however, when VEGF is blocked—in anti-angiogenic therapy, for example—endothelial barrier function is reduced, increasing the likelihood for damage and exposure of the pro-thrombotic surface, which exacerbates the tendency for VTE. Because ATE incidence can escalate during anti-angiogenic therapy through a platelet-dependent mechanism, platelet activation is increased.[11,12]

Bevacizumab

Bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) is a tumor-starving agent designed to block human VEGF-A with an immunoglobulin G1 antibody. The U.S. Food and Drug Administration approved bevacizumab in 2004 for many solid tumors, including metastatic colorectal cancer, non-small cell lung cancer, and kidney cancer. Blocking VEGF reduces the blood supply necessary for tumor cell survival, preventing the regrowth of blood vessels, and may shrink the size of the tumor itself owing to the delivery of insufficient nutrients.[2] Bevacizumab also inhibits the protective function of VEGF, making endothelial cells more susceptible to sdamage and apoptosis;[13] this effect is evident in the toxicities—specifically, thrombosis—that occur during bevacizumab treatment.

Thrombosis Associated with Bevacizumab Treatment

Cancer patients are susceptible to thrombosis, a risk that is further increased by the use of anti-angiogenic therapies such as bevacizumab and chemotherapy. Results from 22 studies (Table 1) show an increased incidence of both ATE and VTE of up to 20% in bevacizumab treatment groups. Two studies[10,14] have shown an increase in ATE but not VTE risk, however, which was not statistically significant. Narlluri et al. have found that the use of bevacizumab in cancer patients was significantly associated with an increased risk of developing VTE.[15] Overall, the incidence of both ATE and VTE in bevacizumab treatment groups is serious enough that it must be recognized and precautions should be taken.

Anticoagulants

Several anticoagulants are currently available for the prevention of thrombosis. Key prophylactic agents include warfarin, low-molecular-weight heparins (LMWHs), unfractionated heparin (UFH), and fondaparinux (an activated factor Xa inhibitor). Significant questions remain, however: which anticoagulation treatment is the most appropriate for cancer patients, and what other agents may increase the risk of thrombosis?

Vitamin K antagonists such as warfarin may be less effective and difficult for many cancer patients to manage. Warfarin has multiple food and drug interac-

Table 1. Risk of Thrombosis and Bleeding with Bevacizumab versus Control (number of patients enrolled).

Study	ATE % (no. patients enrolled)		VTE % (no. patients enrolled)		Bleeding %	
	Bevacizumab	Control	Bevacizumab	Control	Bevacizumab	Control
Allegra et al. 2009[16a]	1.5 (20)[b]	0.8 (11)[b]	6.4 (84)	4.6 (61)	1.9	1.9
Cohen et al. 2007[17c]			5.4 (23)	3.2 (14)		
Escudier et al. 2007[18]	1.5 (5)	<0.7 (2)	3 (10)	<1 (3)	33	9
Giantonio et al. 2007[19]	0.8 (4)[d]	0.4 (1)[d]	3.5 (10)	2.5 (7)	3	< 1
Herbst et al. 2011[20]	3.8 (12)	0.3 (1)			3.2[e]	2[f]
Hurwitz et al. 2004[21]	5.1 (20)	1.3 (5)	19.3 (76)	16.1 (64)	3.1[b]	2.5[b]
Johnson et al. 2004[22]	4.5 (3)	3.1 (1)	15.2 (10)	9.4 (3)	12.5	0
Kabbinavar et al. 2003[23]	4.5 (3)	2.9 (1)	19.4 (13)	8.6 (3)	60	11
Kabbinavar et al. 2005[24]	5.3 (13)	3.0 (7)	17 (42)	17 (40)	5	2
Kabbinavar et al. 2005[25]	10 (10)	4.8 (5)	18 (18)	18.3 (19)	5	3
Kemeny et al. 2011[26]	8.6 (3)[g]	0				
Kindler et al. 2010[27]	2.2 (6)[h]	1.9 (5)[f]	14.1 (39)	15.2 (40)	5	4
Miles et al. 2010[28]	0.4 (2)	0.4 (1)	1.4 (7)	3.5 (8)	1.2	0.9
Miller et al. 2005[29i]	1.3 (3)[j]	3[h]	7.0 (16)	5.6 (12)	29	11
Miller et al. 2007[30k]	1.9 (7)[l]	0[l]	2.2 (8)	1.4 (5)	0.5	0
Moehler et al. 2009[31]	3.4 (1)[m]	0	10.3 (3)	0		
Reck et al. 2009[32n]	2.7 (18)[o]	4.6 (15)[l]	7.1 (47)	6 (21)	4.2	2
Rini et al. 2010[33]	1.4 (5)[p]	0[n]	3.9 (14)	1.7 (6)	5.8	1.2
Robert et al. 2011[34]	1.2 (10)	1.0 (4)	3.7 (30)	3.2 (13)	1.7	0.25
Saltz et al. 2008[35]	1.7 (12)[q]	1.0 (7)[o]	7.8 (54)	4.9 (33)	13	8
Tebbutt et al. 2010[36]	4.4 (14)	0	10.8 (18)	10 (16)	16.2	12
Van Cutsem et al. 2009[37]	3.0 (9)	2.8 (8)	4.7 (14)	18.5 (53)	42	23

[a]Therapy-associated grade ≥3 adverse events not significantly increased. [b]Reported events include cardiac ischemia and central nervous system ischemia. [c]Adverse events occurred at a >2% higher incidence in bevacizumab-treated patients than in control patients. [d]Cardiac ischemia and cerebrovascular ischemia. [e]Grade 3-5. [f]Grade 3-4. [g]1 pulmonary embolism; 2 thrombi caused by Mediport. [h]Cerebrovascular accidents. [i]Grade 1-4 toxicities. [j]Pulmonary embolisms. [k]Grades 3 and 4 toxicities. [l]Cerebral ischemia. [m]Myocardial infarction. [n]Severe adverse effects (grade >3). [o]Includes events reported as myocardial ischemia or infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral ATEs. [p]6Cardiac ischemia/infarction. [q]Includes ischemic cardiac events.

tions that may affect cancer treatments. In addition, patients receiving chemotherapy are likely to have to interrupt anticoagulation therapy owing to chemotherapy-induced thrombocytopenia. Warfarin also has been shown to cause significant increases in the risk of major bleeding compared to that caused by other anticoagulants.[38] Nonetheless, warfarin significantly reduced the rate of VTE compared to placebo in a trial of 311 patients with stage IV breast cancer (0.6% vs. 4.4%; P=0.031).[39]

LMWHs have longer half-lives, greater bioavailability, and more predictable anticoagulant effects than those of many other anticoagulants. In addition, LMWHs require less monitoring while improving survival and decreasing the risk of thrombosis. Many studies have shown that LMWHs are preferred because of their reduced risk of associated thrombosis and reoccurrence compared to that of other anticoagulants.[38,40] LMWH is also implicated in enhanced overall survival through inhibition of angiogenesis. This possible anti-neoplastic effect in cancer may further favor the use of thromboprophylaxis.[40]

The Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients With Venous Thromboembolism (CLOT) trial of 672 patients with active cancer and newly diagnosed, symptomatic proximal deep-vein thrombosis, pulmonary embolism, or

both, compared the LMWH dalteparin to coumarin. The trial showed that cancer patients receiving dalteparin had a 1-year overall reduction in mortality compared to those in the coumarin group (20% vs. 35%), which was statistically significant compared to the warfarin arm of the study (P=0.03).[40] The MEDical patients with ENOXaparin (MEDENOX) study of 1,102 cancer patients found that the incidence of VTE was significantly lower in a group of patients receiving enoxaparin, 40 mg (5.5%), compared to that in patients receiving placebo (14.9%) (P<.001), with no significant difference in bleeding complications41. These results agree with those of the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial of 3,706 immobilized cancer patients in which the incidence of VTE was reduced from 4.96% in the placebo group (73 of 1473 patients) to 2.77% in dalteparin group (42 of 1518 patients; P=.0015) with no significant difference in major bleeding complications.[42]

The PRODIGE study was a randomized placebo-controlled trial determining the efficacy and safety of dalteparin for VTE prevention over a 6-month period in 512 patients with newly diagnosed malignant gliomas. Dalteparin reduced VTE incidence from 15% in the placebo group (n=87) to 9% in the treatment group (n=99) but was associated with an increased risk of major intracranial bleeding (5.1% with dalteparin vs. 1.2% in the placebo group; P=0.2).[43]

The Enoxaparin and Cancer (ENOXACAN) study confirmed that LMWHs and UFH are equally effective and safe for cancer patients. This study compared the LMWH enoxaparin and UFH in a randomized setting in 631 cancer patients. The study concluded that enoxaparin (40 mg daily) was associated with a significantly lower rate of VTE (14.7%) compared to that in UFH (18.2%; 5000 IU 3 times daily) with no increased risk of major bleeding.[44]

With fondaparinux, VTE incidence was reduced to 5.6% in patients without cancer compared to 10.5% in patients administered placebo in the Artemis study. The mortality rate was also reduced to 3.3% in the fondaparinux group vs. 6.0% in the placebo group (P =.06) with low incidence of major bleeding, which was not significant in both groups.[45] The pentasaccharide general surgery study (PEGASUS) compared VTE prophylaxis in 1,408 cancer patients after major abdominal surgery. Patients received either fondaparinux or dalteparin. The result was 4.7% VTE prevalence with fondaparinux and 7.7% prevalence with dalteparin, with no significant major bleeding in the two groups.[46] Thus, fondaparinux proved to be a more effective agent than dalteparin for thromboprophylaxis in cancer patients.

Current Guidelines on Thromboprophylaxis in Cancer Patients

Several evidence-based guidelines are available for thromboprophylaxis in cancer patients (Table 2). The assessment of thrombosis risk in each patient is important. The consensus regarding treatment in patients who are undergoing surgery, immobilized, or hospitalized is generally that thromboprophylaxis is recommended in the absence of any contraindications owing to the higher risk of developing thromboembolic complications.

Cancer patients undergoing a surgical procedure double their risk of postoperative VTE and more than triple their risk of fatal pulmonary embolism compared to patients who undergo surgery for benign diseases8. Ambulatory patients have a lower risk profile of thrombosis, and therefore thromboprophylaxis is not recommended except in patients receiving highly thrombogenic thalidomide- or lenalidomide-based combination chemotherapy regimens.[4]

Only 4% of central venous catheter patients are affected by thrombosis; therefore, thromboprophylaxis is not recommended in this population. Additional risk factors such as prolonged immobility, obesity, and therapy with angiogenesis inhibitors can increase risk in this patient group; hence, consideration of these factors in risk assessments in these patients is vital.[9, 47]

It is important to note that the current guidelines—with the exception of the American College of Chest Physicians (ACCP) guidelines for the general non-cancer population—are limited to the general cancer population and are not specific for cancer patients on bevacizumab therapy. A summary of guidelines for thromboprophylaxis in cancer patients is provided in Table 2.

Thromboprophylaxis for Patients Receiving Bevacizumab

Thromboprophylaxis should be considered in cancer patients receiving bevacizumab, particularly higher-risk patients and those receiving anti-angiogenic therapy, owing to their high risk of thrombosis. Bevacizumab thromboprophylaxis is controversial because of the known bleeding toxicity associated with bevacizumab and anticoagulation therapy. Most studies have shown that bevacizumab administration and prophylaxis with anticoagulants have not increased bleeding risk significantly in cancer patients.

Some studies have analyzed the risk of bleeding

Table 2. Guidelines for Thromboprophylaxis in Cancer.

	ASCO 2007[48]	NCCN1	AIOM/ESMO[47,49]	ACCP 2008[50]
Hospitalized	Yes[a]		Yes in immobilized patients only	
Undergoing surgery	Yes[b,c]	Yes[d]	Yes for major surgeries only[e]	Yes[f]
Ambulatory	Not recommended[g]			Not recommended
CVC	NA	Not recommended		

ACCP, American College of Chest Physicians; AIOM, Italian Association of Medical Oncology; ASCO, American Society of Clinical Oncology; CVC, central venous catheter; ESMO, European Society of Medical Oncology; LMWH, low-molecular-weight heparin; MM, multiple myeloma; NA, not applicable; NCCN, National Comprehensive Cancer Network; UFH, unfractionated heparin.

[a]Thromboprophylaxis with UFH, LMWH, or fondaparinux in absence of contraindications. [b]Thromboprophylaxis is recommended for any major surgery for malignant disease or laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes. [c]Thromboprophylaxis with low-dose UFH, LMWH, or fondaparinux with or without mechanical thromboprophylaxis for the highest-risk patients but not to be used alone unless anticoagulation is contraindicated. [d]Thromboprophylaxis with LMWH, UFH, or fondaparinux with or without mechanical thromboprophylaxis. [e]Thromboprophylaxis with LMWH or UFH. [f]Thromboprophylaxis with LMWH or UFH; for neurosurgery use LMWH. [g]Exception for patients with MM receiving thalidomide- or lenalidomide-based combination regimens.

with anticoagulation therapy, with or without bevacizumab. A recent meta-analysis of 10 studies comprising 6,055 patients given full-dose aspirin anticoagulation therapy for VTE showed a low risk of severe bleeding, and this risk was unaffected by bevacizumab treatment10. In a smaller retrospective review of 29 glioma patients, anticoagulation therapy (warfarin and the LMWH Lovenox) with bevacizumab also showed no association with major symptomatic hemorrhages compared to anticoagulation-only therapy.[51] In a retrospective analysis of 303 metastatic renal cell carcinoma (mCRC) patients from 3 randomized trials, arterial thromboprophylaxis with aspirin and bevacizumab therapy showed no increased prevalence of hemorrhage.[52] In addition, a meta-analysis of 5 randomized controlled trials of 1,745 patients with mCRC showed aspirin to be effective in preventing bevacizumab-induced arterial thromboembolic events with an approximately 1.3-fold increase in grade 3 and 4 bleeding events, which was not statistically significant (P=0.13).[14]

Currently the majority of studies include only therapeutic anticoagulation with bevacizumab, not prophylaxis In the study by Hambleton et al., full-dose therapeutic anticoagulation with warfarin did not increase the rate of hemorrhage in metastatic colorectal cancer patients receiving bevacizumab therapy.[53] A meta-analysis of 3 randomized studies estimated the overall risk of severe bleeding at 4.1% in the bevacizumab group with coadministration of therapeutic anticoagulation with either warfarin or LMWH, and 4.2% patients who received only anticoagulation,[54] suggesting the possibility that full-dose anticoagulation during bevacizumab therapy might be safe.

Other studies have shown an increased risk of bleeding with bevacizumab alone (see Table 1). In a multicenter, randomized double-blind trial of 649 mCRC patients receiving interferon alfa-2a with or without bevacizumab, the bevacizumab group (n=327) had an increase in bleeding of 33% versus 9% in the placebo plus interferon alfa group (n=322).[18] In a study performed by Van Cutsem et al., 306 patients with metastatic pancreatic adenocarcinoma receiving gemcitabine, erlotinib, and bevacizumab had a greater incidence of bleeding (42%) compared to 301 patients receiving gemcitabine, erlotinib, and placebo (23%).[37] These results may indicate that adding anticoagulation to bevacizumab can further exacerbate bleeding risks; however, in both cases, the majority of the bleeding was mainly minor epistaxis.

In summary, these studies have shown that bevacizumab and anticoagulation therapy are associated with no significant bleeding, and they decrease the risk of recurrent thromboembolic events. Because the benefits of anticoagulation therapy outweigh the risks, thromboprophylaxis with bevacizumab should be implemented in clinical practice.

Conclusion

Bevacizumab has proven to be a successful anti-angiogenic therapy for the treatment of solid tumors in cancer patients with or without chemotherapy. Among the consequences of bevacizumab therapy are increased risks for thrombosis and bleeding, however. A limited number of studies on thromboprophylaxis for anti-angiogenesis agents like bevacizumab have been published, and therefore, more studies on bevacizumab and thromboprophylaxis must be designed and carried out. Clinicians must assess risks when considering anticoagulants for the prevention of thromboembolism in patients receiving bevacizumab.

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