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Thromboembolic disease in patients with high-grade glioma

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Venous thromboembolism (VTE) is common throughout the course of disease in high-grade glioma (HGG). The interactions between the coagulation cascade, endothelium, and regulation of angiogenesis are complex and drive glioblastoma growth and invasion. We reviewed the incidence of VTE in HGG, the biology of the coagulome as related to glioblastoma progression, prevention and treatment of thrombosis, and the putative role of anticoagulants as anti-cancer therapy. VTE can be significantly reduced during the postoperative period with adherence to the use of mechanical and medical thromboprophylaxis. Activation of the coagulation cascade occurs throughout the course of disease because of a variety of complex interactions, including tumor hypoxia, upregulation of VEGR expression, and increases in both tumor cell-specific tissue factor (TF) expression and inducible TF expression in numerous intrinsic regulatory pathways. Long-term anticoagulation to prevent VTE is an attractive therapy; however, the therapeutic window is narrow and current data do not support its routine use. Most patients with proven symptomatic VTE can be safely anticoagulated, including those receiving anti-VEGF therapy, such as bevacizumab. Initial therapy should include low molecular weight heparin (LMWH), and protracted anticoagulant treatment, perhaps indefinitely, is indicated for patients with HGG because of the ongoing risk of thrombosis. A variety of coagulation- and tumor-related proteins, such as TF and circulating microparticles, may serve as potential disease-specific biomarkers in relation to disease recurrence, monitoring of therapy, and as potential therapeutic targets.

Keywords: clinical trials, glioma, thrombosis, tissue factor.

This review focuses on the impact of clinical thrombosis during the course of disease in patients with high-grade glioma (HGG), especially glioblastoma. Venous thromboembolism (VTE) is strikingly prevalent and at least as common in glioblastoma as it is in other cancers, such as pancreatic cancer and adenocarcinoma of the gastrointestinal tract. This article reviews the pathogenesis of VTE in the context of brain tumors and the unique complex biology of the tumor cell–endothelium-coagulation system. Evidence-based management of known VTE is reviewed, and the role of short- and long-term is thromboprophylaxis discussed. In addition, the putative role of heparin as an anti-cancer therapy targeting tissue factor and angiogenesis is discussed.

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Incidence/Prevalence

It is well known that the peri-operative incidence of VTE in patients undergoing surgery for brain tumors is high. Estimates of postoperative VTE are typically in the range of 3%–20% depending on the use of thromboprophylaxis and the method of detection.[1–4] In addition, there is continuing long-term risk of thrombosis throughout the course of disease. The postoperative long-term risk of VTE has been reported to be 7%–28% over a 1-year period, with most of these data from retrospective analyses.[5–7] The literature is heterogenous with respect to the definitions and clinical significance of thrombotic events. The detection of a distal venous clot (for example a below-knee occlusion seen on Doppler ultrasound) is not considered to be clinically significant, because many—perhaps most—of these resolve without treatment or sequelae. Reports using routine surveillance with techniques, such as fibrinogen leg scans or Doppler ultrasound, overestimate the incidence of thrombosis by including asymptomatic and non-clinically significant disease.[3] Therefore, recent clinical trials use symptomatically suspected and objectively confirmed proximal Deep vein thrombosis (DVT) and pulmonary embolism as the principal outcomes of interest.

The prospective study by Brandes et al. found that the rate of clinically significant VTE was 0.015 cases per month (18% annually) despite peri-operative heparin thromboprophylaxis.[6] The North American Glioma Outcomes (GO) Project found that investigators recorded VTE in 10.7% of patients at 9–12 months after diagnosis and 22.9% after 12–15 months.[5] In a systematic

review, Marras et al. concluded that the risk of VTE is continuous in patients with glioblastoma, with 1.5%–2.0% risk of events per month of survival.[7] A prospective randomized controlled trial of low–molecular weight heparin (LMWH) thromboprophylaxis in patients with a new diagnosis of HGG detected a cumulative probability of VTE in the placebo control arm of approximately 17% at 6 months after diagnosis.[8] Data from these prospective studies are reasonably concordant and provide estimates for planning future clinical trials testing interventions to prevent development of thrombosis.

Incidence in Comparison with Other Cancers

Estimates of the incidence of VTE consistently show increased relative risk among patients with cancer, compared with the general population and, in particular, greatest risk in patients with adenocarcinomas and glioblastoma. In the UK General Practice Research Database, 151 267 patients with cancer were compared with age-matched control subjects, and 4,755 VTE events (3.1%) were found in the patients with cancer overall.[9] The highest relative risk was seen for pancreas, ovary, and brain cancer (hazard ratio for brain cancer, 10.9; 95% confidence interval [CI], 9.1–13.0). Similarly, a linkage analysis of admitted patients with cancer detected the highest risk for VTE among patients with brain cancer (relative risk, 21.4; 95% CI, 20.4–22.3), compared with cancer overall (relative risk [compared to control subjects], 3.6).[10] Patients with glioblastoma are among the most highly at-risk individuals for thrombosis and its complications in all medical and surgical practice.

Pathophysiology

A variety of patient, tumor, treatment, and humoral factors have been associated with increased risk of thrombosis among patients with HGG (Table 1). Age, medical comorbidity, and prior episodes of thrombosis are risk factors common to VTE in general and, taken together with routine hematological parameters, form the basis of many risk prediction models used in general medicine and surgical practice.[11,12] Particular to HGG are the risks of neurological disability at the time of disease presentation and peri-operative immobility.[2,6] Larger tumors may confer increased risk,[3,13] perhaps because of the presence of higher levels of procoagulant proteins, such as tissue factor (TF). Of course, larger tumors may simply be associated with increased risk of leg weakness either because of direct neurological impairment or as a consequence of dexamethasone requirement and the subsequent development of leg weakness due to myopathy. Risk factors related directly to the presence of glioma include a higher risk of VTE a mong patients with partial resection (and, therefore, residual disease), compared with gross total resection,[14] tumor grade,[3,4] and the presence of intraluminal thrombosis detected in paraffin-embedded surgical tissue,[15] although this is controversial.[16]

Table 1. Risk factors for thromboembolic events in malignant glioma patients

Patient Factors
Age (especially >75)[4]
ABO bloodtype (A, AB)[13]
Prior deep vein thrombosis or pulmonary embolism
Leg paresis, prolonged immobility[2,6]
Multiple medical comorbidities
Obesity
Glioma-associated Factors
Tumor grade (high > low-grade glioma)[3,4]
Intraluminal thrombosis in surgical specimen[15]
Recurrent disease
Tumour size (>5 cm)[3,4]
Post-operative residual disease (biopsy>partial>gross total resection)[14]
Treatment-associated factors
Post-operative period
Chemotherapy[61]
VEGF targeted treatment[38]
Hormonal therapy
Venous access devices
Possible biomarkers
Thrombocytosis, anemia, leukocytosis[62–64]
Activated coagulation factors (D-dimers, thrombin-antithrombin complexes)[62]
Biomarkers to be evaluated further
Tissue Factor (antigen, activity levels, circulated microparticles)[31,32]
Molecular phenotype (EGFRviii overexpression, PTEN loss or mutation)

Treatment of brain tumors can influence the risk of thrombosis. In general, chemotherapy is associated with increased risk of VTE in other solid malignancies and has been found to be an independent risk factor for thrombosis in HGG.[17] Radiotherapy is associated with increased thrombotic risk in various solid cancers, but an association in HGG is unclear, likely because most patients with HGG receive radiotherapy and the risk cannot be compared with an untreated control population. Anti-angiogenic agents are clearly associated with increased risk of thrombosis.[18] Thalidomide was the first anti-angiogenic agent to demonstrate increased thrombotic risk, especially in combination with systemic chemotherapy and dexamethasone;[19] however, thalidomide and its immunomodulatory derivatives, such as lenalidomide,[20] are not commonly used in glioma therapy. Newer anti-angiogenic agents, such a bevacizumab, are discussed later in the artilce.

Activation of the Clotting Cascade

TF, or thromboplastin, is the principal initiator of coagulation. TF is a 47 kD transmembrane glycoprotein with

a long extracellular domain that interacts with Factor VIIa in the coagulation cascade. In physiological conditions, normal vascular endothelium acts as a barrier between cells expressing TF and blood, preventing activation of procoagulant factors. With endothelial damage, the traditional role of TF-Factor VIIa binding leads to activation of the proteolytic cascade, Factor X, and thrombin generation, resulting in fibrin deposition and platelet activation.[21] In additional to this role in coagulation, TF has a shorter cytoplasmic domain, which mediates several downstream signaling effects, including activation and upregulation of VEGF.[22] Constitutive over-expression of TF has been shown in a variety of solid tumors, including glioma,[23] and TF expression is correlated with glioma grade.[24,25]

Tissue factor is implicated in a variety of oncogenic processes, including angiogenesis, cell migration, invasion, and proliferation. Thrombin generated by TF-activation cleaves and activates PAR-1, a G-protein coupled receptor implicated in angiogenesis, including oncogenic signaling via upregulation of EGFR.[23,26] Indeed, common genetic events in glioblastoma, such as PTEN loss and EGFR amplification and over-expression, can lead to TF upregulation through these pathways.[27,28] Increased clotting in tumors has been shown to increase the hypoxic environment and, in turn, to lead to further upregulation of TF. Neoplastic expression of TF appears controlled by 2 well-characterized pathways with relevance to glioma. The mitogen activated protein kinase (MAPK) cascade appears to upregulate TF expression, whereas the pI3-kinase/AKT pathway is associated with reduced TF expression.[29] Mutational activation of K-ras and TP53 loss or mutation leads to upregulation of TF in colorectal cancer.[30] One of the issues hampering translational investigation into the role of TF activation in glioblastoma progression and clinical thrombosis is the lack of a standard assay for TF antigen, activation, or presence in the circulation. Table 2 summarizes some of the notable factors associated with increased TF expression in glioblastoma. These systems remain understudied in glioblastoma, an obvious candidate disease for these molecular correlative studies.

Tissue Factor-Bearing Microparticles

Circulating microparticles (MPs) are detectable in the serum samples from patients with glioblastoma. MPs come from a variety of cellular origins, including glioma cells, endothelium, and bone marrow. In addition to tissue-specific TF, varying forms of TF can be detected in MPs in both healthy control subjects and patients with glioblastoma.[31] Mean MP activity is higher in patients with glioblastoma than in healthy control subjects, and circulating MP levels have been shown to decrease following completion of chemoradiation; furthermore, MP activity may be higher in patients with greater residual tumor burden.[31] Microparticles containing EGFRvIII mRNA can be detected in serum and, when added to endothelial cells in vitro, appear to induce angiogenesis.[32] TF-bearing MPs are an attractive target for further research as a potential marker of glioblastoma activity, a clinical biomarker, and as a therapeutic target. As an example, in other solid malignancies (pancreas, lung, and colorectal cancer), an ongoing phase II trial is selecting patients with elevated TF microparticle activity to select an enriched population for medical thromboprophylaxis with LMWH (NCT00908960).

Table 2. Factors associated with increased tissue factor (TF) expression or activity in malignant glioma

Glioma Grade[25]
Craniotomy[5]
Tumor hypoxia[27,28]
VEGF expression[29]
PTEN mutation/loss[27,28]
EGFR amplification[32]

Peri-operative Thromboprophylaxis

Historically, the risk of ICH limited the use of pharmacological approaches to VTE prevention in patients undergoing neurosurgical procedures. Early ambulation, compression stockings, and intermittent external pneumatic compression devices are strategies shown to reduce VTE, compared with no intervention at all; however, these devices, especially pneumatic compression, are somewhat impractical to implement and offer a small window of opportunity for patients discharged early from acute care.

In neurosurgical patients, in whom up to 80% have CNS malignancy, clinical trials of medical prophylaxis using unfractioned heparin (UFH) or LMWH with compression stockings have shown superiority to mechanical devices alone.[33] In a meta-analysis of 4 studies, a 38% relative risk reduction in favor of UFH/LMWH, compared with mechanical devices alone, was found.[34] Adverse bleeding, including major bleeds, was increased in the heparin arm of this meta-analysis, but the absolute risk increase was low and not considered by expert consensus to be clinically significant. In these studies, UFH or LMWH was started post-operatively, usually 24 h after surgery. A relatively small series suggests that a delay to 48 h is associated with a 25% increase in the risk of thrombosis, whereas pre-operative administration of LMWH leads to an excess of intracranial bleeding.[35] The timing of pharmacological prophylaxis is therefore important. Consensus guidelines from the American College of Chest Physicians recommend post-operative thromboprophylaxis using compression stockings and UFH or LMWH.[36] Prophylaxis should generally be continued throughout hospitalization.

Management of Symptomatic Venous Thromboembolism

Venous ultrasound is the imaging modality of choice for clinically suspected DVT and carries very high sensitivity for the diagnosis of proximal DVT. CT angiography (CTA) is the diagnostic method of choice for suspected pulmonary embolism. Therapeutic anticoagulation with warfarin remains a standard approach to patients with objectively confirmed VTE; however, patients with CNS malignancies have unique management issues, including fear of ICH, medication compliance, and common drug-drug interactions. Common examples of the latter include anticonvulsants, such as phenytoin and carbemazepine; antibiotic prophylaxis with trimethoprim-sulfamethoxazole; and gastrointestinal prophylaxis with agents such as omeprazole.

Despite fears of ICH, it appears to be safe to offer full therapeutic anticoagulation to patients with brain tumors.[17,37,38] Safety in patients with known intratumoral hemorrhage is unknown, but this is a relatively uncommon circumstance. Asymptomatic postoperative blood products do not constitute an absolute contraindication to anticoagulant use for proven symptomatic VTE. Anticoagulation should be initiated as soon as possible after diagnosis of VTE. Consensus guidelines from the American College of Chest Physicians,[39] European Society of Medical Oncology,[40] and the American Society of Clinical Oncology[41] recommend initial therapy with a LMWH drug, such as dalteparin, enoxaparin, or tinzaparin. The basis of these recommendations are 3 randomized controlled trials testing initial therapy with LMWH followed by either warfarin or dalteparin for a total of 6 months of therapy.[42,43] For example, the CLOT trial randomized patients with cancer, including those with HGG, to dalteparin therapy for 5–7 days followed by warfarin (International Normalized Ration, 2.0–3.0 for 6 months) versus 6 months of dalteparin alone (dose-reduced to 75%–80% of full therapeutic anticoagulation during months 2–5).[44] The CLOT results included an impressive reduction in recurrent VTE from 17% to 9% favoring the LMWH arm, without a difference in major bleeding ($P = .002$). This result and similar others support the use of LMWH as a preferred initial therapy for patients with malignant glioma. LMWH is associated with other clinical advantages, compared with warfarin, including no need for laboratory monitoring and minimal drug and food interactions; however, despite these advantages, daily subcutaneous injections and cost present a barrier to widespread use. Patients who are able to be compliant with warfarin dosing and monitoring, who are not on conflicting medications, those with significant renal impairment, or those who cannot tolerate subcutaneous injections may be safely managed with warfarin, acknowledging some increased risk of recurrent thrombosis. Outpatient management of confirmed DVT is generally feasible when using LMWH, especially if patient and caregiver education and teaching are available. Most patients with pulmonary embolism require admission to hospital for supportive care and monitoring. Ideal practice for patients includes an interdisciplinary team with expertise in the management of thrombosis and cancer.

The optimal duration of anticoagulant therapy in patients with cancer is unclear and has not been specifically studied in patients with CNS cancer. Level 1 evidence supports a minimum duration of therapy of at least 3–6 months after diagnosis.[41] Most consensus guidelines recommend indefinite anticoagulation for patients with active cancer or those receiving ongoing chemotherapy. For patients with glioblastoma, where disease is rarely stable for protracted periods, lifelong anticoagulation may be the target goal in many patients. Future study of biomarkers indicating activation of coagulation (such as D-dimers) or underlying biological activity (such as circulating TF) may assist in risk stratification of those patients in whom anticoagulation must be extended, rather than discontinued, over time.

A controversial treatment option in patients with a high risk of bleeding or other contraindications to anticoagulation includes placement of a vena cava filter. Unfortunately, IVC filters are associated with a high failure rate among patients with cancer and in up to 62% of patients with brain tumors.[45] The invasiveness of IVC filters, their inability to treat the hypercoaguable state, lack of proven cost-effectiveness, and issues with recurrent thrombosis[46] are significant drawbacks, and many patients require anticoagulation in due course regardless of their use. If used, it is prudent to use retrievable filter devices and for as short a duration as possible.

Management of VTE During Concomitant VEGF Treatment

Bevacizumab is the first approved antiangiogenic therapy for recurrent glioblastoma. Other VEGF-targeted agents, such as cediranib, pazopanib, sorafenib, sunitinib, vandetanib, and XL-184, are under investigation;[47] this class of therapeutics is likely to remain part of glioblastoma therapy for the foreseeable future. It is likely that these agents increase the risk of VTE among patients with glioblastoma, but the magnitude and clinical significance of any increased risk is unclear and difficult to study given the relatively high baseline incidence of thrombotic events. In addition, because intracranial and intratumoral hemorrhage are part of the natural history of glioblastoma,[48] clinical trials in this context are less likely to detect small but clinically important complications of anticoagulation, such as ICH. In such a context, the detection of signal resulting from increased rates of thrombosis and bleeding requires large clinical trials. Some of the phase I/II clinical trials testing novel agents, such as pazopanib and XL184, have not shown rates of VTE and likely are not more thrombogenic than bevacizumab. Recent larger phase III trials, such as the CENTRIC study testing the addition of cilengitide to standard Radiation/temozolomide, permit patients with known VTE receiving LMWH;

these trials will provide prospective information on the safety of anticoagulation in higher-risk patients.

Nalluri et al. reported a meta-analysis of 7956 patients with advanced non-CNS malignancies who were receiving chemotherapy with or without bevacizumab. Thrombosis of any grade was seen in 11.9% of patients, with a relative risk of 1.33 associated with concomitant bevacizumab use.[19] In the BRAIN trial of bevacizumab with or without irinotecan for recurrent glioblastoma, VTE was seen in 3.6% of patients receiving bevacizumab monotherapy, compared with 8.9% in the combination arm.[49] In the same study, hemorrhage of any grade was 27.4% in the bevacizumab-only patients, with 2.4% intracranial bleeding, compared with 40.5% all-grade and 3.8% intracranial bleeding in the combination arm. As the ongoing large randomized multicenter studies of bevacizumab combined with standard chemoradiation for newly diagnosed glioblastoma (AvaGlio, RTOG 0825) are reported, more precise risk estimates of VTE may become available, especially if study results can be pooled.

Until more data exist, clinicians are reliant on pragmatism with respect to the management of known VTE in patients for whom anti-angiogenic therapy is recommended. Norden et al recently reported a retrospective series of 282 consecutive patients who received bevacizumab at some point during their glioma therapy; of these, 64 (23%) received concurrent therapeutic anticoagulation (80% with LMWH, 20% with warfarin) for an episode of symptomatic VTE.[50] Seven (11%) of patients experienced ICH of any grade, compared with 3% of patients who received bevacizumab without concurrent anticoagulation. Although the absolute rate of ICH was higher and worrisome, there was no increase detected in serious or fatal ICH in this series. The authors reasonably concluded that use of therapeutic anticoagulation is not contraindicated in patients receiving bevacizumab. Unfortunately, the small subgroups in this series did not permit comparison between patients receiving LMWH and those receiving oral anticoagulation. There is little evidence to guide clinicians on whether the use of anti-VEGF agents are safe in patients with glioblastoma already receiving therapeutic anticoagulation for VTE, because many clinical trials of anti-angiogenic agents exclude previously anticoagulated patients. Modulation of anticoagulation intensity can be problematic in neuro-oncology because of common drug-drug interactions. Although warfarin can be safely given to most patients with CNS tumors, it is prudent to recommend use of LMWH rather than oral anticoagulation with warfarin in the subset of patients with glioblastoma who are receiving bevacizumab and other anti-angiogenic agents. Exclusion of patients receiving therapeutic anticoagulation from clinical trials of anti-angiogenic therapy is problematic, because this is both a real-world problem and occurs with a frequency of 20%–30% in glioblastoma. In these studies, the use of LMWH anticoagulation should generally be permitted for patients with symptomatic VTE, anti-platelet agents should be held, and thrombocytopenia screened frequently.

Prevention of VTE: The Role of Primary Thromboprophylaxis

The cumulative risk of VTE is high, making the prevention of thrombosis an attractive goal as part of supportive care for patients with newly diagnosed brain tumors. Long-term mechanical prophylaxis is impractical, and medical prevention with anticoagulant therapy risks development of bleeding, including ICH and intratumoral hemorrhage.

In non-CNS malignancies, several randomized controlled trials and meta-analyses have shown the efficacy and safety of primary thromboprophylaxis, usually with LMWH, in preventing symptomatic thromboembolism.[51,52] Recently, the SAVE-ONCO trial reported a 64% risk reduction in VTE (hazard ratio, 0.36; 95% CI, 0.21–0.60) in patients with cancer who receive chemotherapy, with no difference in bleeding events.[53] In 2012, the Cochrane group reported a systematic review of 9 randomized controlled trials compromising 3538 ambulatory patients with non-CNS cancer enrolled in randomized controlled trials testing primary thromboprophylaxis with a placebo or no-treatment control arm. LMWH was associated with a reduction in the incidence of symptomatic VTE, with a relative risk of 0.62 (95% CI, 0.41–0.93).[51] LMWH was associated with an increase in major bleeding, but this did not reach statistical significance. Although some of the systemic cancer studies testing thromboprophylaxis have included patients with brain tumor, very few have designed only for patients with glioblastoma. Two small prospective studies tested the safety of long-term LMWH prophylaxis in patients with newly glioblastoma (Table 3). Robins et al. reported an ECOG trial that unfortunately was closed prematurely because of the introduction of temozolomide as part of standard upfront therapy.[54] In this study, 45 patients received daily LMWH dalteparin, and no episodes of serious bleeding or VTE were observed. Similarly, in a single-institution study,

Table 3. Prospective clinical trials of primary thromboprophylaxis in patients with newly diagnosed malignant glioma

Study	No. patients, *n*	Medication	Grade 3 or 4 bleeding	Thromboembolic events
ECOG E1FO1[54]	$n = 45$	Dalteparin	None	None
Duke[55]	$n = 40$	Tinzaparin	None	None
PRODIGE[8]	$n = 99$ LMWH	Dalteparin	5 major bleeds (5.1%	9/99 (9.1%)
	$n = 87$ placebo		1 major bleed (1.2%)	13/87 (14.9%)

40 patients were given tinzaparin in an open-label trial, with no bleeding or symptomatic VTE.[55]

The PRODIGE trial, a planned large multicenter, phase III, placebo-controlled trial of LMWH dalteparin prophylaxis in HGG, mostly glioblastoma, was designed to detect a reduction in DVT-free survival at 6 months.[8] This study also closed prematurely, because of lagging accrual and the sponsor's decision not to produce further placebo medication. At the time of analysis, 99 patients were randomized to LMWH and 87 to placebo. A trend to reduction in VTE was seen at 6 months (9 LMWH, 13 placebo; hazard ratio, 0.51; 95% CI, 0.19–1.4), but there were 3 major bleeds in the LMWH arm (all intracranial, one fatal) and none in the placebo arm. Taken together, these studies unfortunately do not resolve the issue of primary prevention in this high-risk population. At present there is no indication for thromboprophylaxis beyond the postoperative period in patients with brain tumors. Identification of clinical factors and biomarkers that predict patients most at risk would greatly assist future studies of medical prophylaxis.

Role of LMWH as a Therapeutic Anticancer Drug

Given knowledge that activation of the coagulation cascade is associated with angiogenesis, upregulation of oncogenic signaling pathways, invasion, and metastasis, it has been hypothesized that anticoagulant treatment may influence tumor biology and improve tumor control, perhaps extending survival.[56] Several clinical trials have evaluated the effect of long-term anticoagulation on survival among patients with various malignancies with promising, but inconclusive results. The first prospective study to consider overall survival as the primary end point was the Fragmin in Advanced Malignancies Outcome Study (FAMOUS).[57] In this trial of 385 patients with advanced cancer, a difference in survival between the dalteparin and placebo arms was not detected; however, a post-hoc analysis found a survival advantage for patients with locally advanced, rather than metastatic, cancer. Since that hypothesis-generating observation, several randomized trials of LMWH prophylaxis have been conducted and have been pooled in a Cochrane library meta-analysis showing a survival advantage for patients with limited-stage disease ($n = 1175$; hazard ratio, 0.77; 95% CI, 0.65–0.91). These encouraging results could not be confirmed in a recently reported randomized controlled trial of LMWH nadroparin in patients with recently diagnosed locally advanced prostate and Non-small cell lung cancer.[58] The jury is therefore still out on the potential therapeutic advantage of long-term anticoagulation as a strategy to improve survival among patients with cancer. No clinical trials have been sufficiently powered to detect differences in survival among patients with malignant glioma; however, the relatively high incidence of VTE in this population coupled with relatively short survival creates an attractive indication for a randomized clinical trial testing LMWH or the newer oral anticoagulants as anti-cancer therapy. It is possible that the seemingly narrow therapeutic window of this therapy, especially the risk of ICH, is dissuading development of pivotal trials in this area.

New Agents

Recent therapeutic developments in the field of thrombosis have focused on factor-specific oral anticoagulants, such as direct inhibitors of thrombin (dibigatran) or factor Xa (rivoroxaban, apixaban, and others); these agents have more predictable pharmacodynamics than warfarin, are used in fixed doses, do not require laboratory monitoring, and are generally free from significant drug interactions.[59] Randomized trials are emerging, and data support their effectiveness for thromboprophylaxis following major orthopedic surgery and for stroke prevention in atrial fibrillation. Thus far, the only agent studied in a population with cancer has been apixaban, which was found to be safe in 125 patients with advanced or metastatic cancer, and no bleeding or VTE events were seen over 12 weeks of therapy.[60] Of course, until further data are available, these newer agents should not be considered in first-line treatment of VTE in CNS malignancies.

Future Research Studies

The complex interactions between the coagulome, proteolytic cascade, angiogenesis, tumor growth, and clinical thrombosis deserve further study. The ideal context to move forward is translational research using tissue and plasma samples in molecular companion analyses to ongoing clinical trials evaluating new approaches to therapy. In particular, the validation of assays for TF and TF-bearing MPs merits attention, as does correlation of these biomarkers with the risk of VTE and clinical outcomes, such as time to progression. Circulating proteins from the coagulation cascade may prove to be helpful biomarkers for disease burden and activity in patients with glioma. If future biomarkers are identified, it may be especially possible to conduct clinical trials testing the role of preventative anticoagulation. Studies enriched through patient selection or biomarker selection may help to reduce the burden of clinical thrombosis in these high-risk patients.

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References

1. Cheruku R, Tapazoglou E, Ensley J, et al. The incidence and significance of thromboembolic complications in patients with high-grade gliomas. *Cancer*. 1991;68:2621–2624.
2. Ruff RL, Posner JB. Incidence and treatment of peripheral venous thrombosis in patients with glioma. *Ann Neurol*. 1983;13:334–336.
3. Sawaya R, Zuccarello M, Elkalliny M, et al. Postoperative venous thromboembolism and brain tumors: Part I. Clinical profile. *J Neuro-Oncol*. 1992;14:119–125.
4. Semrad TJ, O'Donnell R, Wun T, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. *J Neurosurg*. 2007;106(4):601–608.
5. Anderson F, Huang W, Sullivan C, et al. The continuing risk of venous thromboembolism following operation for glioma: findings from the Glioma Outcomes Project. *Thromb Hemost*. 2001;86(Suppl):OC902 (abs).
6. Brandes AA, Scelzi E, Salmistraro G, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. *Eur J Cancer*. 1997;33:1592–1596.
7. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer*. 2000;89:640–646.
8. Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low molecular weight heparin (LMWH) thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost*. 2010;8:1959–1965.
9. Walker AJ, West J, Card T, Crooks C, Grainge MJ. Rate of venous thromboembolism by cancer type compared to the general population using multiple linked databases. *Thrombosis Res*. 2012;129(suppl 1): S155–S156.
10. Arjinian S, Seminog O, Goldacre MJ. Risk of venous thromboembolism after hospitalization with cancer: record linkage study. *Thrombosis Res*. 2012;129(suppl 1):S184–S185.
11. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27:4839–4847.
12. Khorana AA. Risk assessment for cancer-associated thrombosis: What is the best approach? *Thrombosis Res*. 2012;129(suppl 1):S10–S15.
13. Gerber DE, Grossman SA, Streiff MB. Management of venous thromboembolism in patients with primary and metastatic brain tumors. *J Clin Oncol*. 2006;24:1310–1318.
14. Simanek R, Vormittug R, Hassler M, et al. Venous thromboembolism and survival in patients with high-grade glioma. *Neuro-Oncol*. 2007;9:89–95.
15. Rodas RA, Fenstermaker RA, McKeever PE, et al. Correlation of intralumincal thrombosis in brain tumor vessels with postoperative thrombotic complications: a preliminary report. *J Neurosurg*. 1998;89:200–205.
16. Prayson NF, Angelov L, Prayson RA. Microscopic thrombi in glioblastoma multiforme do not predict the development of deep vein thrombosis. *Am Diagn Pathol*. 2009;13:291–296.
17. Jenkins EO, Schiff D, Mackman N, Key NS. Venous thromboembolism in malignant gliomas. *J Thromb Hemost*. 2010;8:221–227.
18. Zangari M, Fink LM, Elice F, et al. Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol*. 2009;27:4865–4873.
19. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA*. 2008;300:2277–2285.
20. Drappatz J, Wong ET, Schiff D, et al. A pilot safety study of lenalidomide and radiotherapy for patients with newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phy*. 2009;73:222–227.
21. Kocaturk B, Versteeg HH. Tissue factor isoforms in cancer and coagulation: May the best isoforms win. *Thromb Res*. 2012;129(Suppl 1): S69–S75.
22. Garnier D, Magnus N, D'Asti E, et al. Genetic pathways linking hemostasis and cancer. *Thrombosis Res*. 2012;129(suppl 1):s22–29.
23. Anand M, Brat DJ. Oncogenic regulation of tissue factor and thrombosis in cancer. *Thrombosis Res*. 2012;129(suppl 1):S46–49.
24. Guan M, Jin J, Su B, Liu WW, Lu Y. Tissue factor expression and angiogenesis in human glioma. *Clin Biochem*. 2002;35:321–325.
25. Hamada K, Kuratsu J, Saitoh Y, et al. Expression of tissue factor correlates with grade of malignancy in human glioma. *Cancer*. 1996;77:1877–1883.
26. Schnaffer F, Yokota N, Ruf W. Tissue factor proangiogenic signaling in cancer progression. *Thromb Res*. 2012;129(Suppl 1):S127–S131.
27. Rong Y, Post DE, Pieper RO, Durden DL, Van Meir EG, Brat DJ. PTEN and hypoxia regulate tissue factor expression and plasma coagulation by glioblastoma. *Cancer Res*. 2005;65:1406–1413.
28. Rong Y, Hu F, Mackman H, et al. Early growth response gene-1 regulates hypoxia-induced expression of tissue factor in glioblastoma multiforme through hypoxia-inducible factor-1-independent mechanisms. *Cancer Res*. 2006;66:7067–7074.
29. Blum S, Issbruker K, Willuweit A, et al. An inhibitory role of the phosphatidylinositol 3-kinase signaling pathway in VEGF-induced tissue factor expression. *J Biol Chem*. 2001;276:33428–33434.
30. Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. *Blood*. 2005;105:1734–1741.
31. Sartori MT, Della Puppa A, Balin A, et al. Prothrombotic state in glioblastoma multiforme: an evaluation of the procoagulant activity of circulating microparticles. *J Neurooncol*. 2011;104:225–231.
32. Skog J, Wurdinger T, van Rijn S, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumor growth and provide diagnostic biomarkers. *Nature Cell Biol*. 2008;10:1470–1476.
33. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective surgery. *N Engl J Med*. 1998;339:80–85.
34. Iorio A, Agnelli G. Low molecular weight and unfractionated heparin for the prevention of venous thromboembolism in neurosurgery: a meta-analysis. *Arch Intern Med*. 2000;160:2327–2332.
35. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep vein thrombosis in patients with brain tumors. *Neurosurgery*. 1998;43:1074–1081.
36. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guideline (8th Edition). *Chest*. 2008;133:381S–453S.
37. Choucair AK, Silver P, Levin VA. Risk of intracranial hemorrhage in glioma patients receiving anticoagulant therapy for venous thromboembolism. *J Neurosurgery*. 1987;66:357–358.
38. Perry JR. Anticoagulation of malignant glioma patients in the era of novel antiangiogenic agents. *Curr Opin Neurol*. 2010;23:592–596.

39. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-based Clinical Practice Guidelines [8th edition]. *Chest*. 2008;133:454S–545S.
40. Mandala M, Falanga A, Roila F. Management of venous thromboembolism [VTE] in cancer patients: ESMO Clinical Practice guidelines. *Ann Oncol*. 2011;22(Suppl 6):vi85–vi92.
41. Lyman G, Khorana A, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol*. 2007;25:5490–5505.
42. Louzada ML, Majeed H, Wells PS. Efficacy of low-molecular-weight-heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials. *Thromb Res*. 2009;123(6):837–844.
43. Lee AY. Treatment of established thrombotic events in patients with cancer. *Thrombosis Res*. 2012;129(suppl 1):S146–S153.
44. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146–153.
45. Levin JM, Schiff D, Loeffler JS, et al. Complications of therapy for VTE in patients with brain tumors. *Neurology*. 1993;43:1111–1114.
46. Schiff D, DeAngelis LM. Therapy of venous thromboembolism in patients with brain metastases. *Cancer*. 1994;73:493–498.
47. Reardon DA, Perry JR, Brandes AA, Jalali R, Wick W. Advances in malignant glioma drug discovery. *Expert Opin Drug Discov*. 2011;6:739–753.
48. Pan E, Tsai JS, Mitchell SB. Retrospective study of venous thromboembolic and intracerebral hemorrhagic events in glioblastoma patients. *Anticancer Res*. 2009;29(10):4309–4313.
49. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27:4733–4740.
50. Norden AD, Bartolomeo J, Tanaka S, et al. Safety of concurrent bevacizumab therapy and anticoagulation in glioma patients. *J Neurooncol*. 2012;106:121–125.
51. Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, Ruties AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database Syst Rev*. 2012;2:CD008500.
52. Rana P, Levine MN. Prevention of thrombosis in ambulatory patients with cancer. *J Clin Oncol*. 2009;27:4885–4888.
53. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med*. 2012;366:601–609.
54. Robins HI, O'Neill A, Gilbert M, et al. Effect of dalteparin and radiation on survival and thromboembolic events in glioblastoma multiforme: a phase II ECOG trial. *Cancer Chemother Pharmacol*. 2008;62:227–233.
55. Perry SL, Bohlin C, Reardon DA, et al. Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients. *J Neurooncol*. 2009;95:129–134.
56. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. *J Clin Oncol*. 2009;27:4902–4911.
57. Kakkar AK, Levine MN, Kadzcola A, et al. Low molecular weight heparin with dalteparin and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol*. 2004;22:1944–1948.
58. Buller H, Prins M, Buller HR, Prins MH. The effect of low-molecular-weight nadroparin on the survival of patients with cancer: a randomized trial. *Thromb Hemost*. 2009;7(suppl 2): LB-MO-004(abs).
59. Verso M, Agnelli G. New and old anticoagulants in cancer. *Thrombosis Res*. 2012;129(suppl 1):S101–S105.
60. Levine MB, Gu C, Liebman HA, et al. A randomized phase II trial of apixaban for the preventon of thromboembolism in patients with metastatic cancer. *J Thromb Hemost*. 2012;10:807–814.
61. Dhami MS, Bona RD, Calogero JA, Hellman RM. Venous thromboembolism and high grade gliomas. *Thromb Hemost*. 1993;70:393–396.
62. Ay C, Vormittag R, Dunkler D, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol*. 2009;27(25):4124–4219.
63. Sawaya R, Glas-Greenwalt P. Postoperative venous thromboembolism and brain tumors: Part II – hemostatic profile. *J Neuro Oncol*. 1992;14:127–134.
64. Sciacca FL, Ciusani E, Silvani A, et al. Genetic and plasma markers of venous thromboembolism in patients with high grade glioma. *Clin Cancer Res*. 2004;10:1312–1317.