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Venous thromboembolism in malignant gliomas

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Summary

Malignant gliomas are associated with a very high risk of venous thromboembolism (VTE). While many clinical risk factors have previously been described in brain tumor patients, the risk of VTE associated with newer anti-angiogenic therapies such as bevacizumab in these patients remains unclear. When VTE occurs in this patient population, concern regarding the potential for intracranial hemorrhage complicates management decisions regarding anticoagulation, and these patients have a worse prognosis than their VTE-free counterparts. Risk stratification models identifying patients at high risk of developing VTE along with predictive plasma biomarkers may guide the selection of eligible patients for primary prevention with pharmacologic thromboprophylaxis. Recent studies exploring disordered coagulation, such as increased expression of tissue factor (TF), and tumorigenic molecular signaling may help to explain the increased risk of VTE in patients with malignant gliomas.

Keywords

bevacizumab; malignant glioma; thromboembolism; tissue factor

Clinical significance of VTE in malignant gliomas

Risk factors and outcomes

The risk of venous thromboembolism (VTE) in adults with malignant gliomas is high; the estimated incidence varies widely and has been reported to be as high as 72%, but is generally accepted to be in the range of 20–30% over the course of the disease [1–6]. The highest risk is in the first few months postoperatively, but the risk of VTE remains higher than other malignancies throughout the course of disease [7], suggesting that increased VTE risk may be a reflection of alternate tumor biology specific to malignant gliomas. In the immediate postoperative period, for example, glioma patients have a higher incidence of VTE than a comparable cohort of colon cancer patients [8,9]. Surgical resection may cause release of procoagulant microparticles (MPs) into the circulation, and post-operative immobility and paresis may further contribute to thrombosis [8,10]. The increased risk of VTE in glioma patients directly attributable to neurosurgery is difficult to quantify because of the lack of standardized prophylaxis methods across available studies; however, one series showed the hazard ratio (HR) for developing VTE was 1.7 [95% confidence interval (CI) 1.3–2.3] within 61 days after neurosurgery [8].

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Established 'generic' risk factors for VTE such as prolonged immobility or indwelling central venous catheter devices can be reasonably extrapolated to contribute to the risk of VTE in malignant glioma. Other risk factors have been confirmed specifically in glioma patients including age greater than 75 (HR 1.8; CI 1.4–2.5) [8]. Proven and possible disease-specific risk factors include glioblastoma (GBM) tumor subtype [5], (HR 1.7; CI 1.4–2.1) [8]; subtotal surgical resection compared with total resection (HR 3.58; CI 0.98–13.13) [6]; glioma size greater than 5 cm (HR 2.2; CI 1.0–4.5) [11]; intraluminal thrombosis in the tumor pathologic specimen [odds ratio (OR) 17.8; CI 4–79.3] [12]; A and AB blood type (HR 2.7; CI 1.0–7.0 and HR 9.4; CI 2.7–32, respectively) [11]; and limb paresis [5,10,13]. Therapy-specific risk factors have also been suggested in glioma patients including treatment with thalidomide [6], and administration of chemotherapy [13]. While radiotherapy is an essential treatment modality for malignant gliomas and has been shown to predispose patients to VTE in other cancers, there are no similar data available for brain tumors. Likewise, corticosteroids are a mainstay of management of vasogenic edema in glioma and are associated with increased rates of VTE in other tumors; however, the role of corticosteroids as an independent risk factor for VTE in malignant glioma patients remains undefined [14].

Bevacizumab (Avastin®; Genentech, South San Francisco, CA, USA) is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody that recently received U.S. Food and Drug Administration approval in recurrent GBM [15]. A well-documented side effect of bevacizumab in extra-central nervous system (CNS) malignancies is intratumoral bleeding [16,17]. Bevacizumab has been linked to an increased risk of arterial and venous thromboembolic events in cancer patients as well [16,18,19]. Thus far, however, there are no data to support the contention that bevacizumab increases the risk of arterial or venous thromboembolism, or indeed intracranial hemorrhage, in GBM patients [20]. In general, composite data from multiple tumor types are inconsistent regarding the risk of thromboembolic events on bevacizumab therapy [21,22], but a recent meta-analysis concluded that bevacizumab is associated with an increased risk of VTE [relative risk (RR) 1.33; CI 1.13–1.56; $P < 0.001$] in non-primary CNS malignancies [23].

In recent years, a great deal has been learned about the epidemiology of VTE in cancer. Thromboembolic events in cancer patients generally portend a worse outcome compared with patients with cancer but without thromboembolic complications [9,24,25]. Furthermore, compared with patients without malignant disease, cancer patients present with larger clot burdens, a greater tendency towards clinical deterioration despite anticoagulation, diminished venographic resolution of the clot despite anticoagulation and a greater propensity for recurrent thromboembolic events after completion of a course of anticoagulation [26]. Cancer diagnosed within 1 year of an episode of VTE correlates with advanced stage and poor prognosis; one study found the 1-year survival of patients diagnosed with cancer and VTE concurrently was 12% compared with 36% in those diagnosed with cancer alone [24]. In addition, hospitalized cancer patients with VTE have a greater in-hospital mortality rate than hospitalized cancer patients without VTE. Finally, the risk of fatal pulmonary embolism (PE) in patients with cancer undergoing surgery is 3-fold greater than that of patients without cancer undergoing similar surgery [21]. Outcomes data for malignant glioma patients are similar; a large neurosurgical cohort showed that patients with VTE had a 30% higher risk of death within 2 years (HR 1.3; CI 1.2–1.4) compared to those without VTE [8].

Management of VTE in malignant gliomas

Historically, physicians have often favored inferior vena cava (IVC) filters over anticoagulation in patients with malignant glioma and VTE because of the perceived high risk of bleeding with anticoagulation [27–29]. However, some authorities suggest that the theoretical risk of bleeding is overestimated, and that anticoagulation can be used safely and

effectively in many instances [2,7,30,31]. The risk of intratumoral hemorrhage on therapeutic anticoagulation is estimated to be 2% [2]. Further, IVC filters carry inherent risks including a higher risk of recurrent VTE, IVC or filter thrombosis and postphlebitic syndrome [1,2,32, 33]. Furthermore, while IVC filters are associated with complications in < 10% of patients without malignancy, in glioma patients complication rates have been reported to be as high as 62% [7,34,35]. Therefore, caution is advised in relying solely upon IVC filters for VTE treatment in cancer patients in whom long-term survival is expected [26].

Absolute contraindications to anticoagulation for VTE are relatively limited. Thrombolytic agents for life-threatening PE are absolutely contraindicated in patients with intracranial malignancy. Some authorities recommend a non-contrast head computed tomography (CT) to rule out active intracranial bleeding prior to initiating anticoagulation in patients with brain tumors and concurrent VTE [1,2,7].

In general, anticoagulation is recommended for at least 3 months after the diagnosis of a first episode of VTE in patients with brain tumors in the absence of any other contraindications. This may be followed by a more prolonged period of less intense anticoagulation with the goal of minimizing the risk of recurrence, depending on a clinical assessment of risks and benefits. Notably, while reported cohort sizes remain small, recent studies have suggested that current anticoagulation for VTE is not necessarily a contraindication to starting bevacizumab despite the theoretically increased bleeding risk associated with this combination of therapies [36].

Thromboprophylaxis

Data from the neurosurgical literature suggest that peri-operative triple thrombosis prophylaxis with graduated compression stockings, pneumatic compression and low-molecular weight heparin (LMWH) or subcutaneous heparin maximizes VTE prevention with a low risk of bleeding [1,37,38]. Given the high risk of VTE in patients with malignant gliomas, outpatient thromboprophylaxis has been proposed. The 2008 ACCP guidelines recommend against primary pharmacologic prevention of VTE in general cancer patients [39]. However, recent studies have shown that anticoagulation administered in usual prophylactic doses slightly increases the bleeding risk and effectively reduces the risk of thromboembolic events [6,40–43]. To date, only one study has examined this issue in malignant glioma patients; the PRODIGE study was a randomized controlled trial designed to determine the efficacy and safety of dalteparin 5000 anti-Xa units or placebo for 6 months for the prevention of VTE in newly diagnosed patients with malignant glioma. This trial was terminated early secondary to expiration of study medication. Preliminary data suggested a trend towards a reduction in VTE incidence in the LMWH group (11% and 17%, LMWH group v. placebo, $P = 0.3$), but with a disconcerting concomitant trend toward an increased risk of major intracranial bleeding (5.1% and 1.2%, LMWH v. placebo, $P = 0.2$) [44]. Therefore, given the seemingly narrow therapeutic window associated with LMWHs, the role of primary prophylactic anticoagulation in this patient population currently remains unclear, and further data are needed to address this important issue.

Validated prediction models to risk-stratify non-CNS cancer patients according to their specific VTE risk have been published, and could be used to select outpatients with cancer for thromboprophylaxis [41,45,46]. However, few patients receiving potentially thrombogenic anti-angiogenic agents such as thalidomide, lenalidomide and bevacizumab were included. While malignant glioma patients were not included in these analyses as a result of limited patient numbers [45,46], one recent study did include glioma patients and showed that elevated d-dimer and prothrombin fragment 1 + 2 (F 1 + 2) identified patients prone to developing VTE and stratified them into low- and high-risk groups [47]. A prediction model combining clinical markers and measurable biomarkers such as circulating d-dimer, F 1 + 2, VEGF or plasminogen

activator inhibitor-1 (PAI-1) levels, as well as tumoral expression of tissue factor (TF) [48–50], could be developed and validated to risk stratify for VTE in malignant glioma patients.

Anticoagulation with LMWH has been proposed to enhance survival through inhibition of angiogenesis and a consequent antineoplastic effect of heparin itself in cancer patients. A recent meta-analysis showed that anticoagulants, specifically LMWHs, both reduced overall mortality in cancer patients without VTE as well as increased bleeding risk [51]. However, these studies all excluded patients with malignant gliomas. A single study examined dalteparin 5000 U subcutaneously (SC) daily with and after traditional radiotherapy in newly diagnosed GBM patients. No significant improvement in survival was noted between treatment and control groups; however, this study was underpowered to resolve this question [52]. Inhibition of coagulation could attenuate cancer progression by decreasing thrombin generation and fibrin formation. Thrombin acts as a potent growth factor and pro-angiogenic factor for cancer cells. Fibrin matrices support migration of tumor cells and provide a scaffold for formation of new blood vessels. Fibrin coats tumors cells and protects them from immune attack, conferring resistance to chemotherapy and mediating attachment to vascular walls, thus enhancing metastasis. LMWH also blocks the adhesion molecules P- and L-selectin, which likely contributes to its anti-angiogenic and anti-metastatic effects in cancer patients [53–56]. The effectiveness of anticoagulation as an antineoplastic strategy remains theoretical, and recent ASCO guidelines conclude that the data are insufficient to support this approach [21].

Pathophysiology of VTE in malignant gliomas

GBM histology

A complex cascade of genetic and cellular events leads to the development of GBM. Genetic events that characterize the transition from lower-grade to malignant gliomas include loss of phosphatase and tensin homolog (PTEN) and VEGF overexpression, two molecular events that have been shown to further up-regulate TF expression [57]. PTEN loss – a genetic signature of glioblastoma rarely noted in lower grade astrocytomas – leads to Akt activation and tumor progression [58]. In GBM, intra-luminal thrombosis is seen in nearly all resected specimens, and the degree of thrombosis correlates with both advanced histologic grade and the subsequent development of VTE [1,12]. Glioblastomas are distinguished from lower-grade gliomas by either necrosis or microvascular hyperplasia, which almost always co-exist. Cells surrounding areas of necrosis are known as ‘pseudopalisading cells’, and they are thought to represent a wave of tumor cells migrating away from a central hypoxic zone created after intravascular thrombosis. These cells secrete pro-angiogenic factors that promote microvascular hyperplasia and tumor expansion. TF expression levels vary within glioblastoma tissues in a pattern consistent with hypoxic regulation with the highest level of expression in hypoxic cells surrounding areas of necrosis. The development of necrosis could be initiated or propagated by vaso-occlusion after intravascular thrombosis within the neoplasm. Both the Ras/MEK/ERK and PI3K/Akt/mTOR pathways are capable of modulating TF expression, particularly under hypoxic conditions; hypoxia has also been shown to induce TF expression via induction of the transcription factor early growth response protein 1 (Egr-1) [59–61]. Vaso-occlusion after intravascular thrombosis could lead directly to the development of hypoxia; the resultant necrosis could be responsible for the induction of the microvascular hyperplasia that defines GBM histology. Factors that may contribute to intra-luminal thrombosis include abnormal blood flow within distorted vasculature, increased interstitial pressure and dysregulation of the balance between pro- and anti-coagulant factors [57,58]. Overexpression of epidermal growth factor receptor (EGFR) in human glioma cells causes increased TF expression, and stimulation of EGFR leads to dose-dependent up-regulation of TF independently of hypoxia [62]. Glioma cells often express a truncated, oncogenic form of EGFR known as EGFRvIII; expression of this form stimulates formation of MPs containing EGFRvIII, leading to increased TF expression, enhanced VEGF production and angiogenesis [63,64]. Oncogenic mechanisms are

responsible for the up-regulation of TF expression by GBM cells; this TF-rich, prothromobotic environment could lead to local thrombosis, necrosis, hypoxia-induced angiogenesis and peripheral tumor growth in gliomas [62]. In fact, a potent exogenous TF inhibitor, Ixolaris, has recently been shown to block the *in vivo* growth of human glioblastoma cells in a xenograft model. Ixolaris may function by both attenuating the procoagulant state, as well as preventing angiogenesis, thus interrupting both tumor growth and metastasis, representing a novel therapeutic target for the treatment of malignant glioma patients [65].

Cellular mechanisms of thrombogenesis

The mechanistic relationship between cancer and thrombogenesis has been extensively studied but remains incompletely understood [66,67]. Tumor-mediated extrinsic vascular compression and invasion can obstruct venous return resulting in clot formation, endothelial injury and activation of the coagulation cascade. Tumor cells may promote thrombin generation by eliciting intravascular TF expression on host monocytes and endothelial cells [26,68]. TF expression is induced by inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α); these factors also downregulate endothelial expression of the anticoagulant protein thrombomodulin leading to a net prothrombotic condition in the vasculature. PAI-1, a member of the serine protease inhibitor (SERPIN) family that inhibits fibrinolysis, is also transcriptionally up-regulated thereby contributing to the pro-thrombotic state [58,69,70].

TF is a target of two of the most common genetic alterations in tumorigenesis, namely inactivation of p53 and mutation of k-ras [71]. TF is a member of the interferon receptor family and it has been described to participate in both regulation of tumor cell growth and stimulation of tumor angiogenesis [70]; inhibition of TF reduces tumor growth in several mouse models [72]. TF may enhance metastatic potential by influencing cellular adhesion and migratory functions [73], and supporting the survival of micrometastases [74]. Tumoral TF expression correlates with advanced clinical stage, histologic grade and poor prognosis in several solid tumor types including gastric, prostate and ovarian malignancies. TF expression has also been shown to correlate with enhanced angiogenesis in several malignancies including hepatocellular, colorectal and prostate cancers, and VTE is 4-fold more common among patients with high TF-expressing carcinomas [16,18,48,49,68,71].

Correlation between enhanced TF expression and advanced histologic grade has also been shown in gliomas [70]. In glioma patients, the combination of TF up-regulation and PAI-1 release can lead to a low-grade disseminated intravascular coagulation (DIC) state [2,68,75]. Elevated PAI-1 levels are seen more prominently in glioblastomas than low-grade gliomas, and its secretion has been correlated with tumor aggressiveness and infiltration of surrounding healthy brain tissue [76]. Glioma patients manifest higher plasma levels of thrombosis-associated biomarkers including D-dimer, lipoprotein (a), homocysteine, VEGF, tissue plasminogen activator (tPA) and PAI-1 relative to patients without glioma, and it has been suggested that these changes contribute to the increased risk of VTE [77,78].

TF expressing microparticles

Normal glial tissue has a very high constitutive expression of TF [68,79,80]. As already described, TF has been shown to function in tumor initiation, tumor growth, angiogenesis and metastasis in glioma cells [63], and a direct correlation between TF levels and tumor grade has been shown in gliomas [70]. The constitutive expression of TF in tumor cells may be augmented by TF expression in host monocytes and vascular cells. TF circulates on small membrane fragments, or MPs, that are shed during cellular activation or apoptosis and may serve to disseminate membrane-bound TF throughout the circulation (Fig. 1). Recent studies have shown that MPs expressing TF (TF-MPs) may be detected in plasma from a variety of cancer

patients, including those with lung, pancreatic, breast and colon cancers; further, the level of TF-MPs may correlate with the risk of thrombosis in these patients [81–84].

TF-MPs account for most of the TF released from cancer cells including glioblastoma cells [85], and tumor cell-derived MPs show strong procoagulant activity *in vitro* and *in vivo* [86]. Together these data suggest a mechanism for the prothrombotic state observed in glioma patients. However, this hypothesis has yet to be supported by data from prospective clinical studies in glioma patients.

Cancer treatment-related procoagulant state

Certain chemotherapeutic agents such as cisplatin have been shown to induce the release of procoagulant TF-MPs from cultured endothelial cells [87]. Bevacizumab, a monoclonal VEGF antibody, highlights the interesting interplay of VEGF and the coagulation cascade in the development and treatment of malignant gliomas. The pathophysiologic mechanisms responsible for the dysregulation of coagulation observed with bevacizumab remain elusive. VEGF regulates vascular proliferation and permeability, and functions as an anti-apoptotic factor. It has been postulated that when bevacizumab inactivates VEGF, the renewal capacity of endothelial cells is diminished resulting in bleeding, whereas the clotting risk is simultaneously increased by enhanced exposure of sub-endothelial collagen and TF [88]. Immune complexes of bevacizumab and VEGF also induce platelet aggregation and degranulation via activation of the platelet FCγRIIa receptor [89]. It has previously been demonstrated that VEGF is capable of transcriptionally activating TF expression in endothelial cells [90,91], and conversely, TF can induce VEGF expression [92,93]. Therefore, high TF expression in some tumor cells may up-regulate VEGF expression, thereby accounting for the observation that high pre-treatment VEGF expression predicts poor clinical outcomes in small cell lung cancer, hepatocellular carcinoma and melanoma patients [94–96]. Consistent with this hypothesis, high-grade glioma specimens show normalization of vascular morphology with the development of thin-walled, evenly distributed vessels after treatment with bevacizumab [16,97].

Conclusions

The risk of VTE in malignant glioma patients is extraordinarily high, and extends beyond the post-operative period. The procoagulant molecule TF appears to play an important role in the pathobiology of GBM including tumor growth, angiogenesis, metastasis and possibly also in thrombogenesis related to it. Thromboembolic events portend a worse outcome in malignant glioma patients relative to those without thromboembolic complications. VTE thromboprophylaxis is utilized with caution in glioma patients because of the concern for intracranial hemorrhage, and additional definition of the risks and benefits of thrombosis prophylaxis is urgently needed. The new anti-angiogenic agent bevacizumab used in malignant glioma is associated with a modestly increased risk of thromboembolism in other forms of cancer; while this risk may also extend to glioblastoma, more data are needed to better delineate this relationship. Additional data are necessary to elucidate the pathophysiology and magnitude of excessive VTE risk, and to evaluate the risks and benefits of primary VTE prevention in malignant glioma patients.

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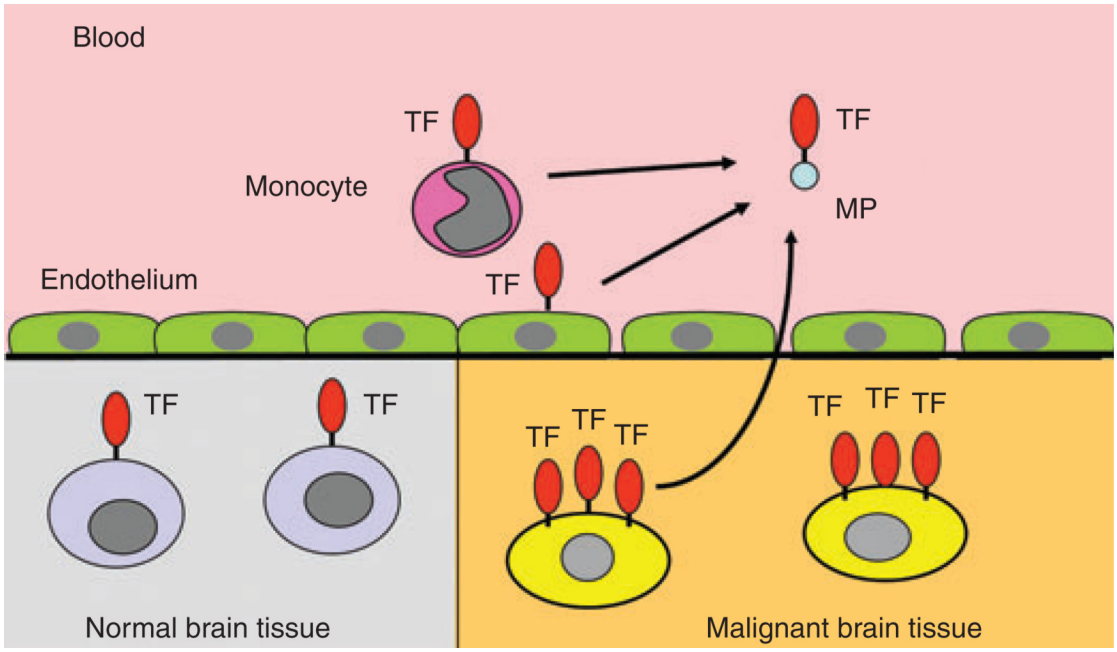

Fig. 1.

Normal brain tissue constitutively expresses tissue factor (TF), and expression is increased on malignant brain tissue cells. In this way, TF may play a role in tumor growth. TF circulates on microparticles (TF-MPs) that are shed during cellular activation or apoptosis. Circulating TF-MPs may be derived from both malignant brain tissue, as well as from upregulated, host cell-derived sources.