Therapeutic Anticoagulation in Patients with Primary Brain Tumors or Secondary Brain Metastasis

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Key Words. Venous thromboembolism • Therapeutic anticoagulation • Malignant glioma • Brain metastasis

ABSTRACT

Patients with primary or metastatic brain tumors are at increased risk of developing venous thromboses. However, the potential benefit of therapeutic anticoagulation in these patients must be weighed against the deadly complication of intracranial hemorrhage. In this review, we summarize available evidence and recent studies of intracranial bleeding risks in primary and metastatic tumors and the impact of therapeutic anticoagulation. We find that for the majority of primary and treated metastatic brain tumors, the risk of spontaneous bleeding is acceptable and not further increased by careful therapeutic anticoagulation with low molecular weight heparin or direct oral anticoagulants, although thrombocytopenia (platelet count less than 50,000/μL) and other coagulopathies are relative contraindications. Patients with brain metastasis from melanoma, renal cell carcinoma, choriocarcinoma, thyroid carcinoma, and hepatocellular carcinoma have a higher tendency to bleed spontaneously than noted in patients with other malignancies, and thus warrant routine brain imaging and alternative strategies such as inferior vena cava filter placement in the acute setting of venous thromboembolism before consideration of therapeutic anticoagulation. *The Oncologist* 2018; 23:468–473

Implications for Practice: Malignant gliomas are associated with increased risks of both venous thromboses and intracranial hemorrhage, but the additional bleeding risk associated with therapeutic anticoagulation appears acceptable, especially after treatment of primary tumors. Most patients with treated brain metastasis have a low risk of intracranial hemorrhage associated with therapeutic anticoagulation, and low molecular weight heparin is currently the preferred agent of choice. Patients with untreated brain metastasis from melanoma, renal cell carcinoma, thyroid cancer, choriocarcinoma, and hepatocellular carcinoma have a higher propensity for spontaneous intracranial bleeding, and systemic anticoagulation may be contraindicated in the acute setting of venous thromboembolism.

INTRODUCTION

Patients with cancer are at increased risk for venous thromboembolism (VTE), and therapeutic anticoagulation is known to decrease VTE's associated mortality and morbidity [1]. The biggest risk of systemic anticoagulation is bleeding, including intracranial hemorrhage, which must be balanced against the recommended chronic anticoagulation for at least the duration of active cancer [1, 2]. As discussed below, those with primary central nervous system tumors and those with tumors that metastasize to the brain have a particularly high rate of VTE. Thus, clinicians often encounter a patient with a brain tumor who requires anticoagulation for a deep venous thromboembolism (DVT) or pulmonary embolism (PE) or for cardiac reasons, such as atrial fibrillation or peripheral vascular disease. As an alternative, an inferior venal cava filter reduces the risk of nonfatal pulmonary embolism, although it does not correct the underlying coagulation defects and can itself thrombose or induce thrombosis of the lower extremity [3]. In recent years, accumulating evidence suggests that anticoagulation can be used safely and effectively in most of these patients [4, 5]. Patients with persistent thrombocytopenia, recent neurosurgery, and tumor types prone to bleeding may require special consideration. In this narrative review, we use three case scenarios commonly seen in the clinical practices of hematologists and oncologists, as well as general internists, to illustrate considerations for anticoagulation in these patients. We summarize available evidence and offer practical algorithms in these situations.

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PATIENT 1

A 42-year-old man with a history of grade III astrocytoma, whose status is after resection and adjuvant radiation and who is now on maintenance temozolomide, presents with macrocytic anemia and peripheral blasts. Bone marrow biopsy reveals acute myeloid leukemia transformed from a background of myelodysplasia. Cytogenetics show an unfavorable inversion of chromosome 3. He is started on decitabine induction chemotherapy. What are the risk factors predisposing this patient to intracranial hemorrhage?

Because it occurs in a closed space, intracranial hemorrhage is one of the most feared complications of cancer and its treatment. Two of the most common causes of bleeding are spontaneous intratumoral hemorrhage and coagulopathy, with less common causes including trauma, hypertension, or hemorrhagic transformation of venous thrombosis [6]. In a large contemporary series of patients with cancer with intracranial bleeding, 68% of patients had solid tumors metastatic to the brain, 16% had primary brain tumors, and another 16% had hematologic malignancies. Intratumoral hemorrhage (61%) and/or coagulopathy (46%) accounted for the majority of cases, whereas bleeding associated with hypertension (5%) was rare [7]. The mechanisms underlying intratumoral hemorrhage include abnormal tumor vasculature, tumor invasion of blood vessels, and tumor cell necrosis [6, 8]. In addition, local imbalances in factors involved in coagulation and fibrinolytic cascades likely contribute directly to intratumoral hemorrhage [9].

The role of platelets in intracranial hemorrhage is less well defined. Thrombocytopenia increases the risk of intracranial tumor bleeding considerably, especially when it is severe (defined as less than 50,000/μL) [10]. Notably, several studies in acute leukemia and other hematologic malignancies have found an elevated prothrombin time, rather than thrombocytopenia, to be more predictive of intracranial bleeding [11, 12]. Nevertheless, an ongoing prospective, nested, case-control study of intracranial hemorrhage in patients with thrombocytopenic hematology will help delineate the exact role of thrombocytopenia and identify additional risk factors for bleeding [13]. Finally, given the potential bleeding risk, the concurrent use of antiplatelet agents during anticoagulation, including nonsteroidal anti-inflammatory drugs, should be avoided if possible.

Patient 1 continued: The patient receives four cycles of decitabine chemotherapy and achieves partial response. His transfusion requirement lessens, and his platelet count is stable above 100,000. However, he complains of left leg swelling, and a left lower extremity venous Doppler ultrasound reveals an acute deep vein thrombosis. Should you initiate anticoagulation?

VTE is highly prevalent in high-grade gliomas, especially around the perioperative period, with a pooled incidence rate of 7%–28% that is among the highest in all cancers [14]. A recent meta-analysis estimated the risk of VTE to be 1.5%–2.0% per month of survival in high-grade gliomas [15]. A myriad of additional VTE risk factors related to the patient, such as immobility, or to the treatment, such as antiangiogenic therapy, have been identified [13, 16]. In addition, tumor-specific factors, such as elevated factor VIII levels, certain ABO blood types, and thrombin generation, were also shown to be risk factors for VTE in patients with glioma [17, 18]. Recently, an elegant biochemical analysis revealed that increased expression of podoplanin, a cell surface glycoprotein, in malignant glioma can trigger platelet aggregation in mouse models, thus contributing to hypercoagulability [19].

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Management of VTE in patients with intracranial malignancies is particularly challenging, due to the fear of intracranial hemorrhage. Although early studies suggested that carefully managed anticoagulation does not appear to increase the risk of intracranial bleeding [20–22], a recent meta-analysis of several retrospective cohort studies indicated an elevated risk of intracranial hemorrhage associated with anticoagulation in patients with glioma (odds ratio 3.75) [5]. This risk increased even further in the setting of supratherapeutic anticoagulation or inadequate preoperative correction of coagulation abnormalities [8, 23]. In more contemporary series, the risk of intracranial bleeding associated with therapeutic anticoagulation in glioma is approximately 4%–5% [5, 24, 25]. Therefore, balancing the risks of thrombosis and hemorrhage is essential, and anticoagulation is generally avoided in patients with a history of previous intracranial hemorrhage, bleeding diathesis, thrombocytopenia (<50,000/μL), coagulopathy, or ongoing life-threatening extracranial bleeding [24]. A recent matched cohort analysis found that the platelets, albumin, no congestive heart failure, warfarin, age, race, diastolic blood pressure, and stroke score for intracranial hemorrhage, initially developed for risk stratification in patients without cancer, accurately predicted intracranial bleeding in patients with malignant glioma [26]. However, this model must be validated by independent datasets before it can be adopted widely.

Anticoagulation with low molecular weight heparin (LMWH) or warfarin is the recommended treatment for established VTE in patients with primary brain tumors [4]. Due to warfarin's significant drug-drug interactions and the need for frequent laboratory monitoring, LMWH has been increasingly used for treatment and prevention of VTE and has been shown to be more effective than warfarin in reducing recurrent VTE [27, 28]. The duration of anticoagulation treatment depends on the continued presence of predisposing factors. An indefinite duration of treatment is generally recommended for patients with primary brain tumor or active systemic malignancy. In patients who are no longer considered at risk for increased hypercoagulability, such as those with grossly resected meningioma, primary central nervous system lymphoma with complete response, systemic malignancies with durable response to chemotherapy, or metastatic germ cell tumors fully treated with chemotherapy, anticoagulation duration is usually 6 months [4, 27].

Finally, patients with thrombocytopenia present an additional challenge for therapeutic anticoagulation. An individualized approach, taking into account the etiology, the severity, the expected duration, and the potential reversibility of thrombocytopenia, is recommended [29]. In the acute setting of VTE, full therapeutic anticoagulation may be initiated at platelet count of ≥50,000 and may be supported by platelet transfusion, whereas in the subacute or chronic treatment periods, dose reduction of LMWH for platelet count <50,000 and

discontinuation for platelet count <25,000 have been endorsed by guidelines [29].

Case follow-up: The patient received therapeutic enoxaparin for treatment of his DVT. However, his acute myelogenous leukemia soon progressed, and he had a brief trial of lenalidomide before enrolling in hospice care.

PATIENT 2

A 69-year-old woman with metastatic non-small cell lung cancer on second-line chemotherapy presents with acute onset dyspnea and chest pressure for 2 days. A chest computed tomography (CT) angiogram shows a segmental PE in the left lower lobe, and a Doppler study reveals a lower extremity DVT. She had brain metastases that were treated with gamma knife therapy, although a brain magnetic resonance imaging (MRI) 1 week ago showed a new, 10-mm frontal metastasis, and she is awaiting additional gamma knife therapy. Should you initiate anticoagulation?

As discussed above, the overall intracranial bleeding risk is usually determined by the presence of prior intracranial bleeding, pre-existing bleeding diathesis (i.e., thrombocytopenia and inherited or acquired bleeding diathesis), and coagulopathy. However, brain metastases from melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma have particularly high propensities for spontaneous hemorrhage in a small case series of 15 patients [30], although brain metastases from other primary tumors (e.g., lung, breast) generally do not bleed spontaneously [4, 31]. In addition, hepatocellular carcinoma also appears to have increased risk of spontaneous intracranial bleeding [32]. In the case of non-small cell lung cancer, a large single-institution series of 776 patients with non-small cell lung cancer with brain metastasis at M.D. Anderson reveals a spontaneous intracranial bleeding risk of only 1.2% over 580 person-years of follow-up [33]. The authors attribute the low rate to the almost universal application of radiation therapy, including gamma knife, which is known to blunt angiogenesis, normalizing tumor vasculature and decreasing the risk of tumor hemorrhage [34].

Several studies have suggested that the risk of tumor-associated intracranial hemorrhage may not be significantly increased in patients with metastatic brain tumors if the degree of anticoagulation is carefully monitored [5]. For example, in a series of 49 patients with intracranial malignancies and VTE who received either inferior vena cava filter (42 patients) or warfarin anticoagulation (15 patients), none of the latter patients had proven hemorrhagic complications, but the complication rate of inferior vena cava filter was higher than commonly perceived and may outweigh the risk of anticoagulation [35]. In another series of 51 patients with known brain metastases and VTE, 3 developed intracranial hemorrhage, 2 of whom had supratherapeutic anticoagulation (above a target international normalized ratio of 2–3). Therefore, therapeutic anticoagulation was more effective than inferior vena cava filter in reducing recurrent VTE [36]. In another large Spanish prospective cohort study of 203 patients with cancer with symptomatic VTE that included 45 with brain metastases, only 1 patient developed an intracranial hemorrhage following anticoagulation with LMWH [37]. Similarly, in a recent large retrospective matched cohort study of 293 patients with brain metastases in which about one third of the patients received therapeutic LMWH, there was no significant difference in the cumulative incidence of intracranial hemorrhage at 1 year among patients

treated with LMWH compared with controls (19% vs. 21% for measurable hemorrhage and 44% vs. 37% for total hemorrhage) [38]. These studies establish LMWH as a safe, and perhaps preferred, anticoagulant for VTE in patients with cancer with treated brain metastasis and without significant coagulopathy or thrombocytopenia. Thrombolytics are considered contraindicated in patients with brain metastasis who present with hemodynamically significant acute PE, although prospective supporting evidence is lacking [39].

The risk of inducing intracranial hemorrhage in a patient with cancer raises questions about whether such patients should undergo brain imaging prior to the use of antiplatelet agents or anticoagulants for VTE or other indications. Unfortunately, there are insufficient data to answer this question, and our practical approach is based upon the risk of brain metastasis being present and the likelihood of such metastases to bleed with anticoagulation. We suggest brain imaging, preferably with MRI, for patients whose primary malignancy is melanoma, renal cell carcinoma, choriocarcinoma, hepatocellular carcinoma, or thyroid cancer, and we suggest that anticoagulation be delayed if brain metastasis is found. Patients with other cancers should also be imaged if anticoagulation can be safely delayed while awaiting imaging or if there are any symptoms suggesting brain metastasis (e.g., headache, mental status changes, seizures, other neurologic symptoms). For patients with occult metastases from other primary tumors, the indication for anticoagulation (e.g., stroke prophylaxis in atrial fibrillation, acute PE, DVT) must be weighed against the risk of hemorrhage. Serial brain imaging during anticoagulation for VTE is currently not supported by prospective evidence, but imaging should be considered in patients with new or changing neurologic symptoms.

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Case follow-up: The patient received therapeutic enoxaparin for treatment of her PE and DVT after a successful gamma knife surgery for her isolated brain metastasis. A repeat MRI 1 month later revealed no signs of intracranial bleeding.

PATIENT 3

A 71-year-old man with metastatic melanoma presents with falls and right lower extremity swelling. A Doppler study shows a DVT in the right femoral vein. Before starting anticoagulation, a noncontrast enhanced head CT reveals several large brain metastases with microhemorrhages and associated vasogenic edema. Targeted therapy and immunotherapy with anti-programmed death 1 antibody have previously failed for this patient. How should we manage the anticoagulation?

Table 1. Anticoagulation considerations in patients with malignant brain tumors

Tumor type	VTE risk	Bleeding risk	AC considerations
CNS malignancies (gliomas)	High	High	AC with enoxaparin or IVCF acutely; once treated, AC with enoxaparin
Secondary brain metastasis (melanoma, RCC, thyroid, HCC, etc.)	High	High	IVCF acutely; once treated, AC with enoxaparin
Secondary brain metastasis (lung, breast, etc.)	High	Low	AC with enoxaparin

Abbreviations: AC, anticoagulation; CNS, central nervous system; HCC, hepatocellular carcinoma; IVCF, inferior vena cava filter; RCC, renal cell carcinoma; VTE, venous thromboembolism.

Patients with malignant melanoma have a high prevalence of brain metastasis and increased risk of spontaneous intracranial hemorrhage. Donato et al. found a significantly higher risk of intracranial bleeding (40%–50% at 1 year) for brain metastases from melanoma and renal cell carcinoma, with or without LMWH [38]. However, a single-institution, retrospective cohort study of 74 patients with melanoma with brain metastases and VTE, in which 57 received systemic anticoagulation, mainly with LMWH, showed that only 2 patients (4%) developed intracranial bleeding [40]. This discrepancy is likely due to the increased sensitivity of modern imaging and longer follow-up in the former study, as well as differences in the radiographic and clinic definition of intracranial hemorrhage. A recent meta-analysis of nine retrospective cohort studies revealed that there was no additional statistically significant increase in intracranial hemorrhage associated with therapeutic anticoagulation in patients with brain metastasis from solid tumors, including melanoma and renal cell carcinoma, suggesting that therapeutic anticoagulation should be considered even for these patients [5].

An acceptable alternative to anticoagulation is the placement of an inferior vena cava (IVC) filter in patients at high risk for intracranial bleeding. However, the use of IVC filters in patients with primary and metastatic brain tumors has been associated with substantial complications, as well as lower efficacy in reducing recurrent VTE [35, 36, 41]. For example, in a series of 42 such patients, 12% had recurrent pulmonary emboli and 57% developed IVC or filter thrombosis, recurrent deep vein thrombosis, or post-thrombotic syndrome [35]. In another series of 51 patients with known brain metastases and VTE, 10 were initially treated with a Greenfield filter (Boston Scientific, Marlborough, MA); 4 (40%) had recurrent nonfatal thromboembolic events (2 PE and 2 DVT), and none of the 39 patients who were initially treated with anticoagulation developed recurrent VTE [36].

Novel direct oral anticoagulants (DOACs) that directly inhibit thrombin (such as dabigatran) or factor Xa, including rivaroxaban, apixaban, and edoxaban, have the advantages of being administered orally, not requiring laboratory monitoring, and infrequent dose adjustment. Overall, these agents appear to have a slightly lower risk of bleeding than warfarin or LMWH in the unselected (i.e., noncancer) population [42]. These agents can effectively treat and prevent VTE but are only now under study extensively in patients with cancer or in comparison with LMWH. In addition, the safety of DOAC use in brain tumors is not well established. Apixaban given for 12 weeks is a safe and efficacious option for the prevention of VTE in ambulatory patients with advanced metastatic cancer undergoing first- or second-line chemotherapy, although the rate of intracranial hemorrhage is unknown [43]. Recently, the first prospective study of rivaroxaban for treating patients with cancer with VTE was reported with acceptable efficacy and safety; however, the rate of intracranial bleeding was not reported [44]. Two recent papers reported cancer subgroup analysis of rivaroxaban and apixaban for treatment of VTE, which showed similar efficacy and reduced rate of bleeding compared with warfarin and LMWH [45, 46]. Given the additional advantage of avoiding self-injection and the increased availability of reversal agents, DOACs will likely see increased use in patients with cancer, although their safety and efficacy in patients with primary brain tumor and secondary brain metastasis warrant prospective investigation.

Case follow-up: Given his limited life expectancy and the high risk of intracranial hemorrhage, Patient 3 received inferior vena cava filter placement for treatment of DVT and salvage whole brain radiation therapy. He maintained acceptable quality of life until passing away 4 months later.

Conclusion

Given the available retrospective and prospective evidence, carefully monitored systemic anticoagulation appears safe in all patients with primary and metastatic brain tumors and VTE, except for patients with untreated tumors with a high rate of intracranial hemorrhage (i.e., metastases from melanoma, choriocarcinoma, thyroid carcinoma, hepatocellular carcinoma, and renal cell carcinoma). LMWH is the preferred agent of anticoagulation over warfarin, given its known safety and efficacy in patients with cancer. The optimal duration of anticoagulation is 6 months, although continuous treatment is recommended for active systemic and/or intracranial malignancies. This is also supported by a recent systematic review and meta-analysis of five prospective trials comparing LMWH with warfarin in patients with cancer with VTE, which found that the overall risk of intracranial hemorrhage was <1% and that anticoagulation with LMWH for ≤6 months did not increase this risk [47].

For patients with metastatic brain tumors that have an increased risk of hemorrhage, it may be appropriate to place an inferior vena cava filter if there is significant untreated disease in the brain, with an understanding that a high rate of complications from these filters is possible. For those whose metastatic disease has already been surgically removed or treated effectively with radiotherapy, systemic anticoagulation may be warranted even for tumors with high bleeding risks. These recommendations are consistent with the published American Society of Clinical Oncology guidelines for the prevention and treatment of VTE in patients with cancer [48], as well as

opinions from other experts in the field [49], and are summarized in Table 1.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

The authors indicated no financial relationships.

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For Further Reading:

Eoin Donnellan, Alok A. Khorana. Cancer and Venous Thromboembolic Disease: A Review. *The Oncologist* 2017;22:199–207.

Implications for Practice:

This article discusses venous thromboembolism (VTE) in patients with malignancy. Practical guidance is offered on how to prevent, diagnose, and treat VTE in cancer patients. The management of "challenging" cases of VTE is also discussed.