

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Prevention and Treatment of Venous Thromboembolism in Primary and Metastatic Brain Cancer



Jeffrey Zwicker, MD
Chief of Benign Hematology Service
Memorial Sloan Kettering Cancer Center
New York, New York

H&O How many people develop brain cancer each year in the United States, and which types of cancer are most likely to lead to brain metastases?

JZ There are approximately 25,000 new cases of primary brain tumors and 200,000 new cases of brain metastatic cancers per year.¹ Brain metastases are most likely to develop in patients with non–small cell lung cancer, occurring in approximately 20% of patients. Brain metastases occur in approximately 5% to 10% of patients with breast cancer, melanoma, or renal cell cancer, and in a smaller percentage of patients with colorectal cancer.

H&O How often do people with brain tumors develop venous thromboembolism (VTE)?

JZ That largely depends on the type of tumor. Glioblastomas are highly associated with thrombosis, with the rate of VTE ranging from 10% to 40% in different cohorts. Cancer with metastases to the brain is less strongly associated with VTE. For example, the rate of VTE is approximately 10% with lung cancer, and lower in patients with melanoma, renal cell carcinoma, breast cancer, or colorectal cancer. Because so many people develop breast or colorectal cancer, these cancer types account for larger absolute numbers of patients with VTE and brain metastasis.

H&O What are the factors that place cancer patients at increased risk for VTE?

JZ Neurosurgery is an established risk factor for VTE, especially in patients with glioblastoma. Researchers are still working to identify which tumor-derived risk factors play a role in who develops VTE. Tissue factor is known to be overexpressed in malignant glioblastoma cells and is thought to play a role in glioma, but this has not been definitively established. Some interesting work has demonstrated that expression of the transmembrane receptor glycoprotein podoplanin on glioma cells may be associated with thrombosis. Podoplanin is expressed on glioma cells and appears to activate platelets directly through the C-type lectin-like 2 (CLEC-2) receptor.

Regarding patients with metastatic disease, the mechanisms are thought to be multifactorial. Tumor-derived risk factors such as tissue factor may play a role. Patients with metastatic disease tend to have worse performance status, which influences the thrombotic risk.

H&O Is there a way to predict which cancer patients will experience VTE?

JZ This is very difficult to predict, especially in patients with primary brain tumors. The best tool we have for estimating VTE risk in patients with cancer is the Khorana score, which factors in body mass index, tumor type,

and complete blood count parameters.² Glioblastoma is known to be associated with VTE but was not included in the original Khorana score model. As such, we do not have prediction models specific to patients with brain tumors. We do know that surgery is a strong risk factor in this population.

The cancer patients at highest risk for intracranial hemorrhage with anticoagulants are those with glioma, metastatic melanoma, and renal cell carcinoma.

H&O When is primary prevention of VTE used in patients with brain cancer?

JZ Because we do not have a good way to predict which patients with brain tumors will develop VTE, we follow the protocols for primary prevention in cancer patients overall. We have data from randomized controlled trials to support the use of direct oral anticoagulants (DOACs) in patients with higher-risk Khorana scores. We also follow recommendations regarding routine thromboprophylaxis in hospitalized patients. Some centers administer extended thromboprophylaxis following surgery for glioblastoma.

H&O What treatment should be used for VTE in patients with brain cancer?

JZ We have a lot of experience using low-molecular-weight heparin (LMWH) for the treatment of VTE in patients with brain cancer, and this has been the standard of care. The use of LMWH in patients with primary and secondary brain tumors was bolstered by several matched retrospective cohort studies that looked at the rates of intracranial hemorrhage (ICH) in patients with brain tumors who received LMWH. We published a cohort analysis in which we compared patients who had brain metastases and developed VTE with those who had brain metastases but did not develop VTE.³ Although the rates of ICH were high among patients in this study, they

did not appear to be higher among those who received enoxaparin vs those who did not receive enoxaparin. We concluded that LMWH can be considered safe to use in patients with metastatic brain tumors.

However, we subsequently found that enoxaparin did increase the risk for ICH in patients with glioblastoma.⁴ One of the questions was whether the increased risk in ICH with anticoagulation in glioblastoma translated to the same risk with DOACs. The phase 3 trials that led to the approval of DOACs enrolled very few patients with brain tumors. The CARAVAGGIO study that compared apixaban with dalteparin for the treatment of cancer-associated VTE specifically excluded patients with primary and secondary brain cancer.⁵

We recently published our experience with DOACs in patients with primary and secondary brain tumors.⁶ DOACs were not associated with an increase in ICH compared with LMWH in the overall patients group. The rates of ICH were similar among those with brain metastases receiving LMWH or a DOAC. DOACs appeared to be safer than LMWH in patients with primary brain tumors, as we did not identify a single case of ICH among patients with glioblastoma who received a DOAC. Caution is warranted because these numbers are still relatively small, but other groups have published similar results. In a systematic review and meta-analysis, the rate of ICH was significantly lower among patients treated with DOACs than with LMWH, at 8.3% vs 11.7%, respectively.⁷

H&O Which cancer patients are at highest risk for ICH with anticoagulants?

JZ The cancer patients at highest risk for ICH with LMWH are those with glioma. Metastatic melanoma and renal cell carcinoma have the highest rates of ICH associated with metastatic tumors. That risk, however, does not appear to be influenced by the administration of anticoagulation. Admittedly, we still need data from larger studies to establish the safety of anticoagulation in these patient groups.

H&O How can hematologists find the right balance between the need for anticoagulation and the risk of bleeding in these patients?

JZ Although we have data to say that anticoagulation can be safely administered to most patients with brain metastases, using either a DOAC or LMWH, it was unsettling to see a 3-fold increased risk for hemorrhage with anticoagulation in patients with glioma in our 2017 study.⁴ We still do not know exactly what the answer is regarding balancing risks and benefits. The emerging data

on DOACs in this population are reassuring.

One important clinical question is what to do when patients experience ICH. We analyzed the outcomes among 79 patients at Beth Israel Deaconess Medical Center with brain tumors who developed ICH while on anticoagulation for VTE. More than two-thirds (68.4%) of the patients restarted anticoagulation after ICH. The rate of a recurrent bleed 12 months after re-initiation of anticoagulation was 6.1%. The size of the incident bleed was the greatest predictor of a recurrent bleed, with the rate of recurrence being 14.5% after a major ICH and 2.6% after a smaller ICH. The rate of VTE was fairly high among patients who did not resume anticoagulation, at 35.3% (compared with 8.1% among patients who restarted anticoagulation).⁸ So we need to carefully consider the balance between preventing VTE and the risk for another hemorrhage.

H&O What about the safety of other antithrombotics in patients with brain tumors?

JZ We have now analyzed cohorts looking at the safety of antiplatelet agents in patients with brain metastases. Reassuringly, we did not identify an increased risk for ICH in patients with brain cancer, at least for patients with brain metastases.⁹ There was actually a signal for improved mortality for patients who were on aspirin, which is a bit counterintuitive because many patients are taking aspirin for cardiovascular disease.

Disclosures

Dr Zwicker has consulted for Parexel, served on the data safety and monitoring board of CSL Behring and Sanofi-Aventis, and received research funding from Quercis and Incyte.

Suggested Readings

1. Cancer stat facts: brain and other nervous system cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. <https://seer.cancer.gov/statfacts/html/brain.html>. Accessed September 12, 2022.
2. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907.
3. Donato J, Campigotto F, Uhlmann EJ, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. *Blood*. 2015;126(4):494-499.
4. Mantia C, Uhlmann EJ, Puligandla M, Weber GM, Neuberger D, Zwicker JJ. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. *Blood*. 2017;129(25):3379-3385.
5. Agnelli G, Becattini C, Meyer G, et al; Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020;382(17):1599-1607.
6. Carney BJ, Uhlmann EJ, Puligandla M, et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. *J Thromb Haemost*. 2019;17(1):72-76.
7. Giustozzi M, Proietti G, Becattini C, Roila F, Agnelli G, Mandalà M. ICH in primary or metastatic brain cancer patients with or without anticoagulant treatment: a systematic review and meta-analysis. *Blood Adv*. 2022;6(16):4873-4883.
8. Carney BJ, Uhlmann EJ, Puligandla M, et al. Anticoagulation after intracranial hemorrhage in brain tumors: risk of recurrent hemorrhage and venous thromboembolism. *Res Pract Thromb Haemost*. 2020;4(5):860-865.
9. Miller EJ, Patell R, Uhlmann EJ, et al. Antiplatelet medications and risk of intracranial hemorrhage in patients with metastatic brain tumors. *Blood Adv*. 2022;6(5):1559-1565.