Thromboprophylaxis in primary brain cancer

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ABSTRACT

Venous thromboembolism (VTE) represents a major source of morbidity and mortality in patients with cancer. Patients with intracranial malignancies, notably high-grade glioma, experience a particularly elevated thrombotic risk. At the same time, these patients are uniquely vulnerable to intracranial hemorrhage (ICH), which may occur spontaneously during the disease course even without exposure to anticoagulant therapy. This competing risk profile creates a significant clinical dilemma, as strategies aimed at preventing life-threatening thromboembolic events may simultaneously increase the likelihood of devastating intracranial bleeding. Consequently, the role of thromboprophylaxis in patients with intracranial tumors remains uncertain. In this review, we critically assess the available evidence on thromboprophylaxis in this population, addressing its risks and potential benefits across diverse clinical settings.

Key words: primary brain cancer; thrombosis; thromboprophylaxis; hemorrhage; anticoagulation.

Introduction

Venous thromboembolism (VTE) is a frequent complication in patients with malignancy and is associated with substantial morbidity and mortality.[1,2] Patients with intracranial malignant tumors, particularly those with high-grade glioma, are considered among the cancer populations at highest risk of thrombotic complications with an estimated VTE incidence up to 30%.[3-5] These patients face a dual hazard: even in the absence of anticoagulation, the risk of intracranial hemorrhage (ICH) is substantial with approximately 6-15% of patients presenting with or developing spontaneous intratumoral bleeding during disease course.[6-8] This risk may increase by an additional 3 to 4-fold in those receiving therapeutic anticoagulation.[6] The use of thromboprophylaxis to prevent potentially life-threatening pulmonary embolism must be carefully balanced against the risk of precipitating potentially fatal intracranial bleeding. As a result, routine thromboprophylaxis in this population is controversial.

In this review, we aim to evaluate the risk-benefit profile of thromboprophylaxis in patients with intracranial tumors across different clinical contexts, including ambulatory versus hospitalized settings, primary and secondary prevention, and the use of thromboprophylaxis following intracranial hemorrhage.

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Prothrombotic and hemorrhagic mechanisms

In the prothrombotic phenotype of primary brain tumors, particularly isocitrate dehydrogenase (IDH)-wildtype glioblastoma, procoagulant tumor-derived microvesicles and the proteins tissue factor and podoplanin are considered to play a key role.[5,9-11] High tissue factor expression by glioma cells initiates the extrinsic coagulation pathway and accelerates systemic thrombin generation, whereas podoplanin expression promotes potent platelet activation and aggregation through engagement of the platelet receptor C-type lectin receptor type-2.[11-13] Whether thrombocytopenia resulting from platelet consumption reflects this hypercoagulable state and may serve as a biomarker for VTE risk remains unclear. Compared with IDH-mutant gliomas, IDH-wildtype glioblastomas exhibit more extensive necrosis, more pronounced hypoxia-driven angiogenesis and a hostile tumor microenvironment.[14] Collectively, these tumor-intrinsic features amplify prothrombotic signaling pathways and likely contribute to the elevated VTE incidence.

Despite this strong prothrombotic drive, patients with primary brain tumors are also predisposed to spontaneous and treatment-associated ICH. In this context, hemorrhage primarily reflects tumor-associated rather than systemic vascular disease, with a central role for aberrant angiogenesis. Increased expression of vascular endothelial growth factor by tumor cells promotes neovascularization and tumor growth, but is associated

with the formation of fragile, highly permeable vessels prone to rupture.[7,11,15] In addition, chronic microthrombi resulting from elevated tissue factor and podoplanin expression, combined with endothelial injury and vessel wall destabilization, may further increase hemorrhagic risk.

Risk of venous thromboembolism and role of anticoagulation

Contemporary clinical guidelines consistently identify patients with primary brain tumors as among the highest-risk malignancies for cancer-associated thrombosis. In patients with high-grade glioma, the incidence of VTE has been reported to reach up to 30%,[3,16,17] with events occurring predominantly within the first six months following diagnosis and/or neurosurgical intervention.[5,9,18] In addition to tumor biology as described above, patient-related characteristics such as reduced mobility and comorbidity and anticancer therapies such as neurosurgery, cranial radiation or antiangiogenic therapy are among the factors that contribute to the high risk of VTE.[3-5,19] To identify patients at highest risk of VTE, several prediction models have been developed over the past two decades, of which the Khorana score, the most widely used clinical tool, has not been specifically validated in the subgroup of glioma patients.[20] Later validation studies have suggested that the use of this score might be extended to this group.[21]

Nevertheless, in a population characterized by a high risk of both thrombosis and bleeding, more dedicated risk-prediction strategies are needed. Given the high baseline risk of a first VTE in all glioma patients, ideally any risk assessment tool would discriminate between patients at relatively "low" and patients at relatively "high" thrombotic risk. Specifically for adult glioma patients, a recently developed and externally validated predictive time-to-event model identified previous VTE, hypertension, asthma, higher white blood cell count, higher glioma grade, older age and increased body mass index as predictors of an increased risk of VTE.[22] When applied to two external validation cohorts, the prediction model demonstrated solid discriminatory performances. The area under the ROC curve ranged from 0.79 to 0.84 in the discovery cohort, and from 0.63 to 0.68 and 0.70 to 0.73 in the two external cohorts, indicating that the model retained moderate predictive accuracy outside the development dataset.[22] It is important to note that predictors may be different for first VTE and for recurrent VTE. Previous studies have estimated approximately 10-30% of patients with glioma to experience recurrent VTE within six months after the first event.[23,24] This risk increases substantially in patients not receiving long-term anticoagulation (hazard ratio of 11.2 [95% CI 1.5-16.3]).[23]

The bleeding risk, particularly ICH, represents the other end of the risk spectrum. In patients with primary brain tumors, the risk of ICH is considerable, even in absence of anticoagulation. Chemotherapy-induced thrombocytopenia, treatment with anti-VEGF agents, and prior or concurrent exposure to radiation, among other therapy-related factors, as well as patient-related factors such as advanced age, renal impairment, or the need for concomitant antiplatelet therapy, can all contribute to an increased risk of bleeding in this population. A previous comprehensive meta-analysis reported an incidence of spontaneous ICH in patients with primary brain tumors of approximately 6-7% in the absence of anticoagulation.[25] This risk doubled almost in patients receiving therapeutic anticoagulation to 12-13%. A meta-analysis of phase 2 trials comparing direct oral anticoagulants (DOACs) with low-molecular-weight heparin (LMWH) showed no increase in intracranial bleeding events, although the subgroup of patients with primary brain tumors was small and the number of outcome events low.[26] The risk of ICH may vary by type of anticoagulation as more recent observational studies show lower rates of ICH associated with DOACs than LMWH.[27,28] Similarly, differences may exist between prophylactically and therapeutically dosed anticoagulation. The available observational studies report outcomes on patients with therapeutically dosed anticoagulation or reduced dose with therapeutic intent.[27,28]

A particular clinical dilemma arises from incidental bleeding events—namely, intratumoral hemorrhages or hemosiderin residues indicative of prior bleeding that are detected on routine imaging in the absence of clinical symptoms. By definition, any intracranial bleeding event is classified as major bleeding, regardless of its clinical presentation. However, the clinical course and outcomes of these asymptomatic hemorrhages remain poorly characterized, despite their importance in guiding subsequent anticoagulation management. In the recently published ABC studies, patients with primary or metastatic brain tumors who had radiographic evidence of hemosiderin deposits on routine imaging continued therapeutic anticoagulation without experiencing recurrent intracranial hemorrhage.[28,29] These findings suggest that incidental bleeding events may not necessarily warrant immediate interruption or discontinuation of anticoagulation, further emphasizing the need for more nuanced risk stratification.

Thromboprophylaxis

Ambulatory setting

Current major clinical guidelines recommend against the routine use of pharmacological thromboprophylaxis in all outpatients with cancer.[30-33] Primary pharmacological thromboprophylaxis can be considered based on an anticipated risk of VTE of 8 to 10% at 6 months, based on validated risk models such as the Khorana score, and in the absence of major contraindications. Although patients with primary brain tumors are at intrinsically high risk for VTE, the concomitant high risk of intracranial hemorrhage, together with limited evidence of net clinical benefit data, renders routine thromboprophylaxis generally inappropriate in the ambulatory setting.

These recommendations are based on clinical trials and predominantly observational studies conducted to date. The PRODIGE trial, a randomized placebo-controlled trial of LMWH thromboprophylaxis in patients with newly diagnosed glioma, demonstrated a reduction in VTE rates, but at the expense of increased ICH in the thromboprophylaxis group.[34] Within six months, VTE occurred in 9 of 99 patients (9.1%) receiving LMWH (dalteparin 5000IU once daily) compared with 13 of 88 patients (14.8%) in the placebo group, corresponding to a hazard ratio of 0.51 (95% CI 0.19–1.4).[34] At 12 months, five intracranial hemorrhages were observed in the LMWH group versus one in the placebo group, all occurring

while patients were on study medication (hazard ratio 4.2, 95% CI 0.48–36).[34]

The AVERT trial, which evaluated apixaban for thromboprophylaxis in ambulatory cancer patients with intermediate-to-high risk of VTE, include a small number of patients with primary brain tumors; 14 of 291 (4.8%) in the apixaban group *vs* 10 of 283 (3.5%) in the placebo group.[35] Outcomes specific to the subgroup of patients with primary brain tumors were not reported separately. Overall, apixaban significantly reduced the risk of VTE compared with placebo (4.2% *vs* 10.2%; hazard ratio 0.41 [95% CI 0.26 to 0.65]), although the incidence of major bleeding was not negligible (3.5% *vs* 1.8%; hazard ratio 2.0 [95% CI 1.01 to 3.95]).[35] Importantly, major bleeding events predominantly occurred in patients with gastrointestinal or gynecological malignancies, with no reports of bleeding in critical organs. The concurrently published CASSINI trial evaluated the efficacy of rivaroxaban 10 mg once daily for thromboprophylaxis in high-risk ambulatory cancer patients; however, since patients with primary brain tumors or brain metastases were explicitly excluded, the results cannot be applied to this group.[36]

In patients with hematological malignancy, thromboprophylaxis has been thoroughly studied in patients with multiple myeloma, who also carry a high thrombotic risk, partly attributable to the use of immunomodulatory agents. In this context, low-dose apixaban appears to be a suitable primary prevention strategy.[37,38] However, given the markedly different bleeding risk profiles between patients with multiple myeloma and those with high-grade glioma, direct comparisons or extrapolation of these findings to patients with primary brain tumors are of limited validity.[39]

Hospitalized setting

Routine pharmacological thromboprophylaxis is recommended for hospitalized patients with cancer in absence of contra-indications.[30-33] For patients with primary brain tumors this recommendation is more nuanced, as all major guidelines consistently emphasize the need for an individualized, multidisciplinary assessment of the risk-benefit ratio. Notably, the 2022 ITAC is the only guideline to explicitly recommend against pharmacological thromboprophylaxis in medically-treated patients with primary brain tumors who are not undergoing neurosurgery.[32]

Patients undergoing neurosurgery for primary brain tumors face a markedly elevated risk of postoperative VTE, driven by factors such as prolonged operative time and extended periods of immobility amongst others.[40,41] In this setting, postoperative pharmacological thromboprophylaxis is currently recommended as part of a combined strategy that also includes mechanical prophylaxis to reduce VTE risk. A previous randomized trial of 307 patients undergoing elective neurosurgery demonstrated that LMWH (enoxaparin in prophylactic dose) in combination with compression stocking reduced the rate of VTE from 32% to 17% (relative risk of 0.52, 95% CI 0.33 – 0.84).[42] Here, intracranial bleeding occurred in 3% of each group. Interestingly, a recent randomized controlled trial involving 283 patients undergoing elective, prolonged neurosurgical procedures demonstrated that initiation of LMWH in the preoperative period, rather than postoperatively, was associated with improved outcomes.[43]

Number needed to treat *versus* number needed to harm

Prevention of first VTE with prophylactic anticoagulation

In absence of strong evidence from clinical trials, it is only possible to make assumptions about the potential risks and benefits of thromboprophylaxis in the outpatient setting, extrapolating from data in other tumor types. Prophylactic anticoagulation in high-risk ambulatory cancer populations is generally associated with a relative reduction in VTE risk of approximately 50%.[44] Approximately 10-20% of patients with primary brain tumors, but without established previous venous thrombosis, develop VTE over the disease course, mainly in the first 6 months after diagnosis.[8,17,45] Importantly, most available incidence data pertain to patients with glioblastoma. For other high-grade gliomas, primary central nervous system (CNS) lymphoma, and mixed malignant CNS neoplasms, the limited data suggest a somewhat lower risk of first VTE.[17,18,46]

Assuming a baseline first VTE risk of 15% in patients with glioblastoma, 12% for other high-grade gliomas and primary CNS lymphoma, and a 50% relative risk reduction with anticoagulation, the estimated number needed to treat (NNT) to prevent one VTE would be ~13 for glioblastoma and ~17 for other high-grade gliomas and primary CNS lymphoma. Such NNTs would generally be considered low enough to consider thromboprophylaxis.[33] Based on extrapolated data from the PRODIGE and AVERT trials evaluating prophylactic dalteparin and apixaban, we estimate that any prophylactic-dose anticoagulation increases ICH risk by approximately 3% (NNH ≈ 33). Specifically, dalteparin is associated with a 3.9% absolute increase in ICH risk (NNH = 26), whereas apixaban shows a 1.7% increase (NNH = 59). On a purely quantitative basis, these estimates suggest a net clinical benefit in favor of prophylactic anticoagulation. From a clinical perspective, however, the potential consequences of ICH, including severe neurological morbidity and high short-term mortality, are generally considered more serious than those associated with VTE events. Although the case-fatality rate of VTE appears to be higher than that of major bleeding in cancer patients receiving anticoagulation, this has not been specifically studied for ICH.[47]

Accordingly, current leading guidelines recommend against routine primary thromboprophylaxis in ambulatory patients with primary brain tumors in the absence of established thrombosis.

For the considerations above to move beyond extrapolations towards robust evidence, future studies will need to directly assess the incidence, severity, and outcomes of ICH associated with prophylactic-dose anticoagulation in patients with primary brain tumors. Although oral anticoagulants are attractive from a patient-centered perspective, additional safety data are required to adequately assess the net clinical benefit in this setting.

Prevention of recurrent VTE with therapeutic anticoagulation

In patients with primary brain tumors with a history of VTE, the risk of recurrence is substantial, particularly in the absence of long-term anticoagulation. We approximated the risk of recurrent VTE at 30%.[23,45] Assuming that therapeutic anticoagulation con-

fers an 80-90% relative risk reduction, the absolute risk of recurrence is reduced to 3-6% while on treatment. This corresponds to an absolute risk reduction of approximately 25% with an NNT of about 4 to prevent one recurrent VTE event.

In parallel, data from meta-analyses indicate that therapeutic anticoagulation increases the risk of intracranial hemorrhage from about 6.5% without anticoagulation to 12.5% with anticoagulation, corresponding to an absolute risk increase of 6% and a NNH of approximately 17 for any ICH.[6,25,48] In the context of secondary VTE prevention, these NNT and NNH estimates suggest a net clinical benefit of therapeutic anticoagulation despite the associated increase in bleeding risk. This interpretation aligns with current guideline recommendations, which endorse therapeutic anticoagulation in patients with primary brain tumors and established VTE, while emphasizing the importance of careful, individualized assessment of bleeding risk. Several recent observational studies and meta-analyses of observational data further suggest a lower risk of ICH associated with DOACs compared with LMWH in patients with primary brain tumors.[25,27,28] The recently published APICAT trial demonstrated better safety and comparable efficacy of prophylactically dosed apixaban during the extended treatment phase in patients with VTE and active cancer. However, its findings cannot be directly extrapolated to patients with primary brain tumors, given the distinct pathophysiology underlying intracranial hemorrhage in this population. Nonetheless, these results further underscore the need for dedicated clinical trials evaluating optimal anticoagulation dosing in this high-risk population.[49,50] As factor XI inhibitors are currently being evaluated in clinical trials, individualized anticoagulation risk assessment will remain essential, although emerging therapeutic options may render this balance somewhat less challenging in the future.[51]

Prevention of VTE after intracranial hemorrhage

Optimal anticoagulant strategies following intracranial hemorrhage remain uncertain. Evidence from small retrospective studies suggests that prophylactic-dose low-molecular-weight heparin may be considered in selected patients, as the markedly increased risk of recurrent VTE in the absence of any anticoagulation is consistently highlighted.[27,52,53]

Perspectives: current and future

A nuanced approach to anticoagulation in patients with primary brain tumors remains essential. Therapeutic anticoagulation is indicated for patients with established VTE, with direct oral anticoagulants increasingly emerging as the preferred option when clinically appropriate. However, robust clinical trial data are still needed to evaluate the safety profiles of available anticoagulants across different dosing strategies. Improved identification of patients at the highest risk for both thrombosis and bleeding may facilitate the development of a fast-and-frugal decision tree to guide individualized thromboprophylaxis strategies.[54]

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