Venous thrombosis in patients with high-grade glioma

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Purpose of review
High-grade glioma (HGG) patients are at particularly high risk of venous thromboembolism (VTE) occurrence and recurrence. VTE is associated with worsened survival in these patients. At present, the main challenge when prescribing anticoagulants in HGG patients is to address the risk of intracranial hemorrhage and provide the optimal treatment.

Recent findings
Here, we discuss the latest biological findings and their potential implications for better classification in daily practice and stratification of patients in future trials according to their risk of developing a VTE.

Summary
To help clinicians, international guidelines have been provided for cancer patients, but their implementation remains suboptimal. We report here the specificities of VTE management in HGG patients relative to other cancer patients. Particular aspects such as anticoagulation under targeted therapies, primary and secondary prophylaxis, and the role of new oral anticoagulants are discussed as well.

Keywords
brain tumor, deep venous thrombosis, glioblastoma, high-grade glioma, pulmonary embolism

INTRODUCTION

High-grade glioma (HGG) patients display one of the highest relative risks of venous thromboembolism (VTE) among cancer patients, with observed rates as high as 25–39% [1,2]. VTE is associated with worsened survival in glioblastoma (GBM) patients [1]. The main concern when prescribing a prophylactic or curative antithrombotic treatment in HGG patients is the risk of intracranial hemorrhage (ICH). In this review, we discuss the epidemiology, currently identified risk factors, and therapeutic management of VTE in HGG patients. Specific situations such as treatment of VTE occurring under anti-vascular endothelial growth factor (VEGF) therapy, primary and secondary prophylaxis, and the role of new oral anticoagulants are discussed as well.

EPIDEMIOLOGY

The incidence rates have been most frequently described within a range of 7.5–39%, with the lowest rate reported in a retrospective assessment, thus probably underestimated, and rates of 17–18% observed in recent prospective studies with a diagnosis based on a combination of clinical and ultrasound Doppler assessments [1–6]. Even if the probability of VTE occurrence is particularly high in the postoperative period, with nearly half of the events occurring at that time, the risk persists throughout the course of the disease, with rates between 7 and 28% over a 12-month period [1,2,7–12]. A recent retrospective study reported that 22.2% of the unplanned readmissions of GBM patients within 30 days of surgery were related to VTE [13▪]. These patients had twice the risk of mortality compared with other patients.

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KEY POINTS

- The presence of active intracranial symptomatic bleeding is an absolute contraindication to curative anticoagulation.
- Curative anticoagulation should be prescribed for a minimum of 6 months; then the decision to stop or continue anticoagulation should be based on cancer activity, performance status, benefit–risk ratio, and the patient's preference.
- LMWHs are preferred to other anticoagulants due to their excellent therapeutic index and lack of interaction with chemotherapy, steroids and antiepileptic agents.
- The concomitant use of bevacizumab and LMWHs at curative doses in GBM patients appears to be well tolerated.

RISK FACTORS

Among many identified risk factors that can be divided into patient-related, tumor-related, and treatment-related, leg motor impairment seems the most consistently reported, with a relative risk for VTE between 2.6 and 3.6 [9,11,14,15]. The other patient-related, identified, preoperative, independent factors include poor Karnofsky Performance Scale (KPS) scores, older age (≥65 years old, especially >75 years old) [5,9,14], elevated BMI [2], hypertension [9], hemoglobin [2], and A or AB blood type [16]. Tumor-related factors include a higher grade (GBM > WHO grade 3 glioma > WHO grade 2 glioma) [9,11], larger size (>5 cm) [10], and recurrent disease. The role of intraluminal thrombosis remains controversial [17–19]. Treatment-related risk factors include the extent of surgical resection [biopsy > partial > gross total resection (GTR)] [2], surgery duration for more than 4 h [20], recent neurosurgery (<2 months), chemotherapy [7], and anti-VEGF agents [18,21]. D-dimer elevation above 0.865 mg/l and/or hemiparesis were factors found to predict a VTE 4 weeks before its clinical outcome in GBM patients under bevacizumab [21].

IDENTIFICATION OF PREDICTIVE BIOMARKERS

A recent study identified the following biomarkers in HGG patients: platelet count, D-dimers, sP-selectin, factor VIII (FVIII) activity, prothrombin fragment 1 + 2, and leukocyte count [22▪▪]. Only the first three parameters have been confirmed in multivariate analyses. Platelet count was inversely correlated with VTE risk, which is a completely new observation that differs from previous studies on other malignancies that report a high platelet count as a risk factor [23]. A low platelet count with high sP-selectin puts patients at high risk of postsurgery VTE (83.3%) [22▪▪]. A risk assessment model (RAM) based on low platelet count (<25th percentile), high leukocyte count, and increased D-dimers (≥75th percentile) was also used. The patients scoring 2 or 3 were considered at high risk (37.7%) of developing VTE, whereas patients scoring 0 were at low risk (3.3%) of developing the disease. Further validation of these data is needed. High levels of FVIII – a validated risk factor for VTE [24] – were already previously found to be predictive of VTE in HGG patients [25] They may be caused by tumor-mediated cytokine release, vascular injury, and surgical disruption of the blood–brain barrier.

BIOLOGY OF VENOUS THROMBOEMBOLISM IN BRAIN TUMORS

The coagulation system is continually activated in GBM, where intratumoral vaso-occlusive thrombosis may trigger hypoxia, pseudopalisading necrosis, and angiogenesis.

Tissue factor (TF) has been shown to be constitutively overexpressed in glioma, and thus has been suggested to play a central role in the pathogenesis of VTE [7]. An increased expression or activity of TF in glioma has been previously associated with glioma grade [26], craniotomy [12], tumor hypoxia [27,28], VEGF expression [29], PTEN mutation/loss [27,28], and epidermal growth factor receptor (EGFR) amplification [30]. The prothrombotic action of circulating microparticles, in which TF derived from glioma cells is present, remains controversial [31–33]. Nevertheless, circulating microparticle levels have been shown to diminish after completion of chemoradiotherapy, and microparticle activity may be superior in the case of greater residual tumor burden [31]. A better understanding of the TF pathway and its effect on HGG behavior and microenvironment is essential to define the exact role of anticoagulants in brain tumor management.

VENOUS THROMBOEMBOLISM RISK ASSESSMENT AND PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

Because the benefit of prophylaxis increases with the risk of VTE, improved prediction of the risk is crucial. A periodic assessment of VTE risk, based on a validated assessment tool, has been recommended in cancer patients [34–37].

It is commonly accepted that hospitalized patients who have an active malignancy with an

acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of contraindications [38–41]. This recommendation applies to HGG patients. The decision to initiate prophylactic anticoagulation with low-molecular-weight heparin (LMWH) in patients suffering from intratumoral bleeding complicated by functional impairment and immobilization should be discussed on a case-by-case basis. This decision should rely on the evaluation of the benefit–risk ratio between worsening of the bleeding and the occurrence of a VTE.

During the perioperative period, the administration of LMWH or unfractionated heparin in combination with mechanical methods, such as pneumatic compression stockings, appears to be effective and reduces risk of postoperative VTE by 50% at least [42▪]. This method is well tolerated and does not cause any increased risk of major ICH despite a two-fold higher rate of minor bleeding [3,42▪,43–45]. Nevertheless, safety has been shown under the condition that anticoagulation is started within 24 h after surgery, because the risk of clinically significant ICH has been shown to be increased if anticoagulants are initiated before neurosurgery [43,46]. This timing is specific to neurosurgical patients [34,38]. In cancer patients, the minimal advised duration of the postsurgical primary prophylaxis is at least between 7 and 10 days. However, in the case of prolonged immobilization or restricted mobility caused by functional impairment, prophylactic anticoagulation should be prolonged until ambulation is recovered. A combination of mechanical and pharmacologic prophylaxis is advised because it improves the efficacy of treatment in high-risk patients [38,42▪,47▪]. It remains uncertain whether the HGG patients could benefit from an extended postoperative prophylaxis, like in the case of high-risk cancer patients to whom 4 weeks are advised [38]. Further investigations are required.

Outside of the perioperative period and hospitalization, long-term prophylactic anticoagulation is not recommended due to a lack of available data in the literature.

To assess this specific situation, the PRODIGE trial was designed to evaluate the potential role of LMWH (dalteparin) in GBM patients and specifically detect a reduction in VTE-free survival at 6 months [48]. A total of 186 patients were randomized into two groups of treatment (dalteparin vs. placebo) until the premature termination of the trial was caused by a shortage of the placebo. Dalteparin was administered during a minimum period of 6 months, which could be extended to a total of 12 months. A lack of power may explain why statistical significance was not present despite the difference observed between the two groups in terms of clinically relevant VTE incidence (11% with dalteparin vs. 17% with placebo). At 12 months, the incidence of major ICH was higher in the dalteparin group (5 vs. 1%; NS), with one fatal ICH. Two phase II studies addressed this question in HGG patients.

In the Eastern Cooperative Oncology Group study, also interrupted prematurely, 45 patients received dalteparin during a median time of 6.3 months, without any occurrence of VTE or ICH [49].

In another study, tinzaparin was assessed in 40 patients. A 2.5% rate of VTE and of ICH was observed after median treatment duration of 5 months [50].

A controlled, randomized, triple-blind, multinational phase III study is planned and will assess the role of the oral factor X blocker apixaban over a 12-month period in newly diagnosed GBM. The primary endpoint is overall survival [51].

No data support the safety and efficacy of the use of aspirin in the long-term prophylaxis of VTE in patients with HGG, and consequently, this approach cannot be advised [52].

TREATMENT OF SYMPTOMATIC VENOUS THROMBOEMBOLISM

There is no standardized approach for the management of HGG patients suffering from a VTE because most existing international guidelines address cancer patients in general. Here, we discuss the specificities characterizing the management of such patients.

Bleeding-risk assessment

Although the anticoagulation of VTE at a curative dosage appears to be well tolerated in most HGG patients, a preassessment of the risk of bleeding and its consequences in terms of neurological worsening is advised to establish the expected risks and benefits prior to any treatment decision [7,53]. This risk is considerably different according to the histological type of the tumor, natural past history of bleeding, and the nature of the concomitant anticancer treatment administered to the patient. In HGG, the reported risk of spontaneous hemorrhage is typically between 2 and 8%, with higher rates in GBM, and anaplastic oligodendroglioma [14,54,55].

Contraindications to anticoagulation and indications of inferior vena cava filters

Pre-existing postsurgical intraparenchymal blood products in asymptomatic patients do not contraindicate anticoagulant use for documented symptomatic VTE [56].

Anticoagulation at curative doses should be avoided in the case of recent significant intratumoral symptomatic bleeding, thrombopenia under 50 000 platelets/μl, and for any other usual contraindication such as coagulopathy [34,38]. When anticoagulants cannot be prescribed at curative doses, the insertion of inferior vena cava (IVC) filters is a possible option, despite a known high rate of complications that include up to a 40% rate of recurrent VTE, filter thrombosis, and post-thrombotic syndrome [57]. In addition, physicians should be aware that caution should be applied in patients with recent brain surgery, those at high risk for falls, and those who are expected to show poor compliance to treatment, especially in the case of oral medication [38]. Unfortunately, all of these mentioned situations are frequent in the population of neuro-oncology patients due to sensory motor, visual, balance, and cognitive deficits.

Which anticoagulant?

According to several retrospective and prospective series, LMWH appears to be well tolerated in the curative setting in patients with HGG [1,57]. LMWH does not interact with other drugs frequently prescribed for brain tumor patients and does not require any frequent monitoring for therapeutic activity. The efficacy of LMWH was superior to that of vitamin K antagonists (VKAs) with no increased risk of ICH in the CLOT trial [58].

In HGG patients, several retrospective series have shown an acceptable profile of tolerance for warfarin without any significant increase in the risk of ICH under the conditions that the international normalized ratio (INR) remains in the therapeutic range and that the perioperative period is avoided [14,52,59]. As a matter of fact, the careful monitoring of the INR needed to maintain warfarin in the therapeutic range is difficult to implement in daily practice because INR variations are subject to many interactions with chemotherapy, steroids, and some antiepileptic drugs. These variations expose patients to risks of both VTE recurrence (infratherapeutic range) and ICH (supratherapeutic range), and thus consequently to the discomfort of very frequent laboratory blood sampling to evaluate the INR.

New oral anticoagulants, such as direct inhibitors of thrombin or factor Xa, have not been evaluated in this specific population, and one should be aware of the absence of an antidote in the case of a clinically relevant ICH. Other concerns include potential drug interaction with chemotherapy and antiepileptic agents and the inability to measure the anticoagulant activity in daily practice [34]. For these reasons, these agents cannot be currently advocated in neuro-oncology patients [56,60]. Further specific studies are needed.

Initial therapy should be initiated as early as possible, once contraindications are ruled out, and should consist of LMWHs [34,38,40,41,56,58,61]. A close monitoring without dose adjustment is recommended in specific situations such as central nervous system malignancies, elderly patients and patients at high risk of bleeding [34,38,61].

Duration of anticoagulation

Duration of anticoagulation or secondary prophylaxis is an important topic because prevention of VTE recurrence may have a significant impact on the survival of cancer patients [62]. This hypothesis relies on the observation that survival was significantly decreased in cancer patients with recurrent VTE, particularly when a pulmonary embolism occurred [62]. The optimal duration of curative anticoagulation in cancer patients remains controversial. A minimum of 6 months of anticoagulation is commonly recommended. After 6 months, the decision to stop or continue anticoagulation should be based on an individual assessment of cancer activity, benefit–risk ratio, and patient preference. More often, it is recommended to prolong anticoagulation as long as the cancer is active and chemotherapy is administered, regardless of the risk of ICH. In HGG patients, this means that most patients will receive an anticoagulant until the end of their life. Some of the guidelines allow VKA replacement after 3 months, with a targeted INR of 2 to 3 when LMWH is contraindicated or not available for any other reason including patient preference. In this situation, VKA should always be preferred to any new oral anticoagulant for the reasons mentioned above, and warfarin is the only VKA that has been extensively studied.

Management of venous thromboembolism during bevacizumab administration

Bevacizumab is a monoclonal antibody targeting VEGF, which has received US Food and Drug Administration (FDA) approval for recurrent GBM. Whether this agent increases the risk of venous thrombosis is still debated [18,63]. On the contrary, a potential increase in the risk of ICH has initially raised great concern regarding the use of bevacizumab in this population. In GBM, the risk of ICH under bevacizumab is not significantly increased, with rates between 0 and 3.8% [64,65]. For oligodendroglioma patients, who are slightly more prone to bleeding, a 24% ICH rate has been reported under bevacizumab, but only 4% of patients were

symptomatic and needed the treatment to be discontinued [66].

Uncertainties have also been raised regarding how to manage brain tumor patients with a diagnosed VTE under bevacizumab. Few data (retrospective only) are available regarding the concomitant use of bevacizumab and anticoagulants at curative doses in GBM patients with a VTE [53,56,59]. Nevertheless, the risk-to-benefit ratio seems to favor this combination despite an increased risk of ICH (from 3 to 11%) [53,67,68]. Once the anticoagulation has been initiated at an effective dose, it is not clear how long bevacizumab should be interrupted before being reintroduced.

CONCLUSION

Despite a high incidence of VTE and recurrent VTE in HGG patients, there is no standardized approach to the management of these patients, and many challenges remain. Nevertheless, most of the international recommendations for VTE in cancer patients can be applied, and some of those specifically address problems encountered in HGG. Nevertheless, a preassessment of the risk of ICH is advised prior to any treatment decision, and a close monitoring of these patients is advised. The duration of prophylaxis and curative anticoagulation is an important matter that remains to be addressed because it may affect patients' survival.

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Conflicts of interest

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