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Full Length Article

Recurrent venous thromboembolism in glioblastoma

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ABSTRACT

Background: Patients with glioblastoma (GBM) are at increased risk of initial and recurrent venous thromboembolism (VTE) but rates of recurrence and real-world treatment choices are incompletely understood.
Objectives: We aim to describe the treatment of incident VTE, report incidence and risk factors for recurrence.
Patients/methods: We conducted a retrospective cohort study of consecutive Cleveland Clinic patients with GBM presenting with objectively diagnosed deep vein thrombosis (DVT) or pulmonary embolism (PE) from 2007 to 2013 with at least 6-month follow-up. We collected information on patient demographics, VTE incidence, treatment and recurrence. Data were analyzed using multivariate logistic regression analysis.
Results: Of 450 patients with GBM, 145 (32.2%) developed VTE and comprised the study population. Of these, 11 (7.6%) experienced PE, 117 (80.7%) had DVT and 16 (11%) had DVT as well as PE. Fifty five (37.9%) VTE events occurred in the first 30 post-operative days and 56 (38.6%) during chemotherapy. Thirty one (21.4%) patients were untreated. Treatments included enoxaparin (N = 36, 24.8%), warfarin (15, 10.3%) or vena cava filters either alone (N = 39, 26.9%) or in combination with anticoagulation (N = 21, 14.5%). Recurrent VTE occurred in 39 patients (26.9%).In multivariate analysis, lack of long term anticoagulation (HR 11.2, CI 1.5–86.3, $p < 0.05$) and the presence of second primary malignancy (HR 3.69, CI 1.2–11.1, $p < 0.05$) were significantly associated with recurrent VTE.
Conclusion: VTE and recurrent VTE are highly prevalent throughout the disease course among patients with GBM. Long term anticoagulation is associated with reduced risk of recurrent VTE but is often not utilized.

1. Introduction

Venous thromboembolism (VTE) is a common complication of glioblastoma (GBM) [1]. The incidence of symptomatic VTE among patients with GBM ranges between 3 and 60% depending on the methods of detection and modalities of thromboprophylaxis employed [2,3]. A prospective randomized control trial of thromboprophylaxis in the setting of high grade glioma reported 17% incidence of VTE in the placebo arm within the first 6 months of diagnosis [4]. While the risk of thrombosis is highest post operatively, the risk of VTE remains elevated throughout the course of the disease with 1.5–2% risk of events per month of survival [5]. While the incidence of recurrent thrombosis ranges between 11 and 17%, risk factors for recurrence are incompletely understood [6,7].

There is a wide range of therapeutic options for patients with VTE in the setting of GBM. The American Society of Clinical Oncology (ASCO) guidelines recommend administration of anticoagulation with careful monitoring given the known risk of bleeding, if the risk of recurrent or progressive thrombosis is greater than that of hemorrhage [8]. The glioma prophylaxis study cited above reported a 5.1% incidence of intracranial bleeding in the arm receiving low molecular weight heparin (LMWH) at prophylactic doses [4]. With a relative scarcity of good evidence, clinicians are uncertain about how best to balance risks and benefits of anticoagulation in this setting.

In this study, we describe our experience with recurrent VTE in GBM in the contemporary era of antiangiogenic therapy. In this, the largest such series to date in the literature, we describe the incidence, profile the characteristics of patients with VTE and also compare modalities employed for prophylaxis and treatment. We aim to characterize the incidence and risk factors for recurrent VTE in the setting of GBM.

2. Materials and methods

The Cleveland Clinic is an academic medical center providing patient care in a nonprofit group practice setting. It is among the five largest

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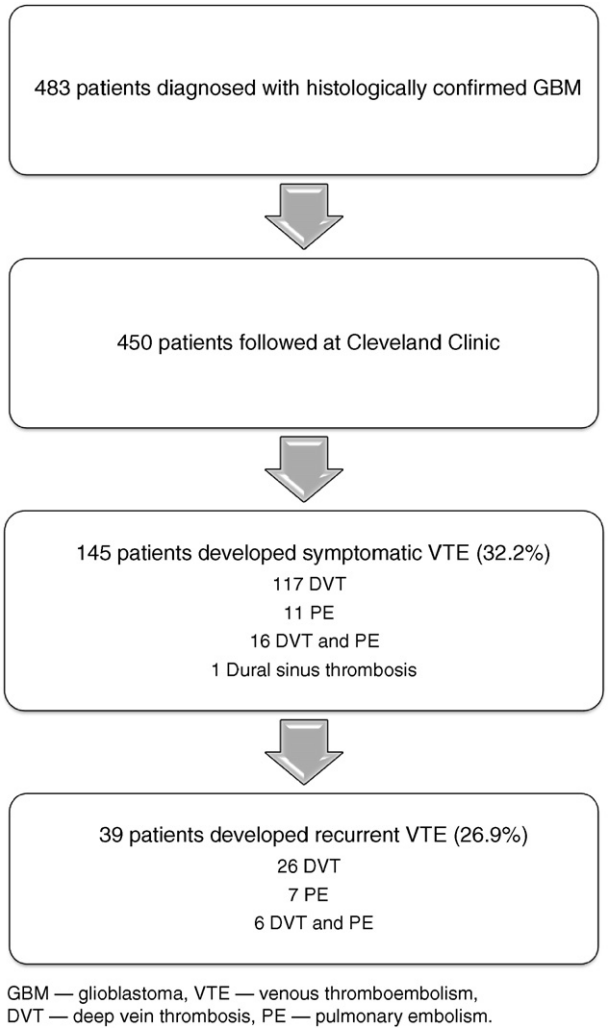

Fig. 1. Flow sheet of patients with VTE in the setting of GBM.

group practices in the US. The Rose Ella Burkhardt Brain Tumor and Neuro-Oncology center records over 8000 patient visits and 900 surgeries each year.

Cleveland Clinic pathology records were queried to obtain medical record numbers of consecutive adult patients presenting between 2007 and 2013 with a histologic diagnosis of GBM. We reviewed individual patient electronic medical records for each identified patient specifically reviewing radiology reports for evidence of documented VTE. VTE events included deep vein thrombosis (DVT) confirmed by extremity ultrasonography and pulmonary embolism (PE) confirmed by computerized tomography (CT) and cerebral sinus thrombosis as detected by magnetic resonance venography (MRV). The study cohort comprised all patients with confirmed VTE (Fig. 1).

Variables collected included demographic information and disease specific information such as type of surgery, IVC filter placement etc. Treatment history including history of anticoagulant use and thromboprophylaxis was obtained through review of the prescription history and medication administration record. We also collected data regarding objectively diagnosed recurrent VTE. We defined recurrent thrombosis as new deep vein thrombosis or pulmonary embolism at a site distinct from the index VTE that developed after the index thrombosis.

Data was extracted by NE, a resident physician, through direct review of the patients' electronic medical record for inpatient and ambulatory visits.

While the Cleveland Clinic has a Thrombosis service, clinical care of patients with GBM is provided by the Oncology service. The majority of patients in our study were not managed by the Thrombosis service and we did not use any database maintained or operated by this service. Regardless of primary team, all thrombotic events would be documented on the electronic medical record. It is possible but unlikely that patients receiving care at the Cleveland Clinic would be managed for thrombotic events at another center outside of the Cleveland Clinic network.

In order to ensure capture of all VTE events, we excluded patients who did not maintain a minimum of 6 months follow-up at Cleveland Clinic. Patients with spinal glioblastoma were not included.

Patient characteristics were summarized using frequencies for categorical variables and by using medians and ranges for continuous variables. Categorical variables were compared using the chi square test. Continuous variables were compared using Student's t test. Variables that were found to be significantly associated with VTE were fitted into a multivariate logistic regression model undertaken to determine the contribution of individual variables to the overall risk. Analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2014).

3. Results

A total of 483 patients had been reviewed at our center. We excluded 33 of these based on the fact that they presented only for a single visit and obtained ongoing care elsewhere. Of 450 GBM patients, 145 (32.2%) developed VTE and formed the study population. Baseline characteristics of the patients are described in Table 1. The age of the patients ranged from 39 to 94 years with a median of 67 years. Eighty-five (58.6%) patients were male.

Second primary cancers were seen in 16 patients (11%). All of these were diagnosed prior to diagnosis of GBM (range 5–20 years, median 7 years) Five patients had a history of prostate cancer, one patient had a history of prostate cancer as well as sarcoma and one patient had a history of dermatofibrosarcoma. Two patients had previously diagnosed breast cancer and one had previously treated breast cancer along with anaplastic T cell lymphoma. Three patients had history of renal cell cancer. One patient had a history of colon cancer and two others had head and neck malignancies.

3.1. Characteristics of VTE events

Of 145 patients with confirmed VTE, 11 (7.6%) experienced PE and 117 (80.7%) developed DVT (Table 2). Thirteen patients (8.9%) were known to have VTE prior to the diagnosis of GBM. Sixty six (45.5%) of

Table 1
Baseline characteristics of patients with VTE in the setting of GBM.
VTE — venous thromboembolism, GBM — glioblastoma.

Characteristics	Median (range)	N (%)
Age (years)	67 (39–94)	–
Body mass index	29 (15.6–45.1)	
Gender	–	
Male		85 (58.6)
Female		60 (41.4)
Comorbid illnesses	–	
Chronic kidney disease		1 (0.7)
Chronic obstructive lung disease		7 (4.8)
Congestive heart failure		2 (1.4)
Smoking	–	2 (1.4)
Second primary malignancy		16 (11)
Tumor size (largest dimension in cm)	4 (0.9–8.5)	–
Karnofsky performance status	80 (10–100)	
Type of surgery		
Biopsy	–	56 (38.6)
Near total resection		12 (8.3)
Subtotal resection		43 (29.7)
Gross total resection		34 (23.4)