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Venous thromboembolism in patients with glioblastoma multiforme: Findings of the RIETE registry

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ABSTRACT

Background: There is uncertainty about the optimal therapy of venous thromboembolism (VTE) in patients with glioblastoma multiforme (GBM).
Methods: We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) database to compare the rate of VTE recurrences and major bleeding during the course of anticoagulation in patients with GBM, other cancers and in patients without cancer.
Results: As of September 2014, 53,546 patients have been recruited in RIETE. Of these, 72 (0.13%) had GBM and 11,811 (22%) had other cancers. Most patients in all 3 subgroups received initial therapy with low-molecular-weight heparin (LMWH), but those with GBM received slightly lower doses than those with other cancers or without cancer. Then, most patients with GBM continued on LMWH for long-term therapy, at similar doses than those in the other subgroups. During the course of anticoagulation (mean, 202 days), 3 patients with GBM presented VTE recurrences (10.9 per 100 patient-years; 95% CI: 2.76–29.5) and 4 suffered major bleeding (one intracranial) (14.5 bleeds per 100 patient-years; 95%CI: 4.60–34.9). Compared with patients with other cancers, those with GBM had a similar rate of VTE recurrences and major bleeds, but had a higher rate of extracranial hematoma ($p < 0.05$). Compared with VTE patients without cancer, those with GBM had a higher rate of PE recurrences ($p < 0.01$) and major bleeding ($p < 0.001$), particularly extracranial hematoma ($p < 0.001$).
Conclusions: Patients with GBM and VTE had a similar rate of VTE recurrences or major bleeds during the course of anticoagulant therapy than those with other cancers.

1. Introduction

Patients with central venous system malignancies have a substantial risk for developing both thrombotic and bleeding disorders. The risk of venous thromboembolism (VTE) is substantially higher in these patients, both in the perioperative period and throughout their disease course. These patients harbor a latent hypercoagulability, which predisposes to VTE, as do postoperative immobility, hemiparesis, and other factors. Using the UK Clinical Practice Research Database, the incidence rate of VTE was compared in 83,203 patients with cancer and in 577,207 age-matched control subjects without cancer. VTE events were found in 3352 (4.0%) patients with- and in 6353 (1.1%) without cancer [1]. The highest relative risk was found for pancreas, ovary or brain cancer. In another study using the Rochester epidemiological database, all cancer sites had an increased standardized morbidity ratio, ranging from 4.1 for head neck cancer to 47.3 for brain cancer [2]. Glioblastoma multiforme (GBM) is the most aggressive malignant primary brain tumor in adults. It is a highly vascularized tumor, and the advent of angiogenic inhibitors has been associated with an increased risk of VTE and bleeding [3–7]. The management of VTE in these patients is complex, given the significant morbidity and mortality associated with

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intratumoral bleeding. The perceived risk of intracranial bleeding limits the use of anticoagulation for the management of VTE with many doctors favoring the use of inferior vena cava filter only for treatment [8,9].

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) initiative is an ongoing, multicenter, international (Spain, Argentina, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia, Switzerland, and Venezuela enrolled patients) observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE. It started in Spain in 2001, and some years later the database was translated into English aimed to expand the Registry to other countries, ultimately allowing physicians worldwide to use the database to select the most appropriate therapy for their patients. Data from this registry have been used to evaluate outcomes after VTE, such as the frequency of recurrent VTE, major bleeding and mortality, and risk factors for such outcomes [10–15]. The current study used the RIETE database to compare the rate of major bleeding and VTE recurrences during the course of anticoagulant therapy in patients with GBM versus those with other cancers and in patients without cancer.

2. Methods

Consecutive patients with symptomatic acute VTE confirmed by objective tests (contrast venography or ultrasonography for suspected deep vein thrombosis [DVT], pulmonary angiography, lung scintigraphy or helical computed tomography scan for suspected PE) were enrolled in RIETE. Patients were excluded if currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study-coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

2.1. Study design and outcomes

For this analysis, cancer patients with newly diagnosed cancer (less than 3 months earlier) or with cancer being treated by either surgery, chemotherapy, radiotherapy, hormonal, support therapy or combined treatments, were considered. Major outcomes were the rate of VTE recurrences and major bleeding. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal. Secondary outcomes were all-cause death, fatal PE and fatal bleeding. Fatal PE, in the absence of autopsy, was defined as any death appearing within the first 10 days after PE diagnosis (either the initial PE episode or recurrent PE), in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

2.2. Baseline variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: patient's gender, age, and body weight; presence of coexisting conditions, concomitant medications and additional VTE risk factors including recent immobilization (defined as non-surgical patients confined to bed with bathroom privileges for ≥4 days in the 2-months prior to VTE diagnosis) and surgery (defined as an operation in the 2 months prior to VTE) were recorded. Moreover, recent (<30 days prior to VTE) major bleeding, clinical characteristics of the malignancy (cancer site, staging, cancer duration since diagnosis), laboratory data on admission and treatment details (including drug, dose and duration of anticoagulant therapy) were also recorded.

2.3. Treatment and follow-up

Patients were managed according to the local clinical practice of each participating hospital i.e., there was no standardization of anticoagulation treatment. During each visit after onset of VTE, either in hospital or in the outpatient clinic after discharge, any signs or symptoms suggesting VTE recurrences or major bleeding during the course of anticoagulant therapy were noted. Clinically suspected recurrent VTE was investigated by repeated imaging as appropriate according to local physician practice.

2.4. Statistical analysis

Categorical variables were reported as percentages and compared using the chi-square test (two-sided) and Fisher's exact Test as appropriate. Odds ratios and corresponding 95% confidence intervals were calculated, and a p value < 0.05 was considered to be statistically significant. Continuous variables were compared with a Student t test. Incidence rates were calculated as cumulative incidence (events/100 patient-years). Statistical analyses were conducted using SPSS for Windows Release (version 20, SPSS Inc. Chicago, Illinois).

3. Results

As of September 2014, 53,546 patients with acute VTE have been recruited in RIETE. Of these, 72 (0.13%) had GBM and 11,811 (22%) had other cancers. Patients with GBM were significantly younger and less likely had chronic lung disease or anemia, but more likely had recent surgery (36% vs. 14%) or immobility (32% vs. 19%) than those with other cancers (Table 1). Moreover, patients with GBM had earlier occurrence of VTE after diagnosis of cancer, and were more likely receiving corticosteroids at VTE presentation (70% vs. 13%) but less likely were to be using antiplatelet drugs. The proportion of patients initially presenting with PE was similar in both subgroups. As to the treatment of cancer, patients with GBM more likely received radiotherapy (41% vs. 9.6%) than those with other cancers. Compared with patients without cancer, those with GBM were more likely men, less likely had chronic lung disease and more likely had recent surgery. They more likely were taking corticosteroids but less likely received antiplatelets (Table 1).

The duration of anticoagulant therapy was significantly shorter in patients with GBM (median: 96 days) than in the other two subgroups (median: 133 and 185 days, respectively), as shown in Table 2. Most patients in all 3 subgroups received initial therapy with LMWH, but those with GBM received slightly lower doses (164 ± 48 IU/kg/day) than those with other cancers (175 ± 43 IU/kg/day) or without cancer (179 ± 39 IU/kg/day). Then, the majority of patients with GBM continued on LMWH for long.-term therapy, at similar doses than those in patients with other cancers or without cancer.

During the course of anticoagulation (mean, 202 days), 3 patients with GBM presented VTE recurrences (10.9 per 100 patient-years; 95% CI: 2.76–29.5), 4 suffered major bleeding (one intracranial) (14.5 bleeds per 100 patient-years; 95% CI: 4.60–34.9) and 34 died (122; 95% CI: 85.8–168), as shown in Table 3. Compared with patients with other cancers, those with GBM had a similar rate of VTE recurrences and major bleeds, but had a higher rate of extracranial hematoma ($p < 0.01$) and

Table 1
Clinical characteristics of VTE patients with glioblastoma, other cancers or no cancer.

	Glioblastoma	Other cancers	No cancer
Patients, N	72	11,811	41,663
Clinical characteristics			
Gender (male)	44 (61%)	6378 (54%)	19,772 (47%)*
Age (mean years ± SD)	64 ± 11	69 ± 13†	65 ± 19
Body weight (kg ± SD)	77 ± 15	72 ± 14†	76 ± 16
Underlying conditions			
Chronic lung disease	2 (2.8%)	1412 (12%)*	4697 (11%)*
Chronic heart failure	1 (1.4%)	725 (6.1%)	2936 (7.0%)
CrCl levels (mg/dL ± SD)	86 ± 36	70 ± 108	77 ± 37*
CrCl levels <60 mL/min	21 (29%)	5009 (42%)*	15,340 (37%)
Platelet count <100,000/μl or >450,000/μl	26 (36%)	4889 (41%)	12,870 (31%)
Anemia	22 (31%)	6710 (57%)‡	11,537 (28%)
Recent major bleeding	2 (2.8%)	335 (2.8%)	817 (2.0%)
Additional risk factors			
Immobility ≥4 days	23 (32%)	2214 (19%)†	10,373 (25%)
Recent surgery	26 (36%)	1678 (14%)‡	4398 (11%)‡
Estrogen use	1 (1.4%)	374 (3.2%)	2383 (5.7%)
None of the above	25 (35%)	7806 (66%)‡	25,466 (61%)‡
Prior VTE	9 (12%)	1652 (14%)	6729 (16%)
Concomitant therapies			
Corticosteroids	50 (70%)	1468 (13%)‡	2438 (6.3%)‡
Chemotherapy	34 (49%)	4781 (40%)	–
Radiotherapy	29 (41%)	1129 (9.6%)‡	–
NSAIDs	3 (4.3%)	637 (5.8%)	2264 (5.9%)
Antiplatelets	2 (2.9%)	1457 (13%)†	5907 (15%)†
Cancer characteristics			
Time to VTE (months ± SD)	6 ± 7	12 ± 26‡	–
Time to VTE (median months-IQR)	3 (1–9)	8 (2–37)‡	–
Metastases	4 (5.7%)	4988 (42%)‡	–
Initial VTE presentation			
Pulmonary embolism	40 (56%)	5961 (50%)	21,037 (50%)

Differences between patients with other cancers or without cancer versus those with glioblastoma: *p < 0.05; †p < 0.01; ‡p < 0.001.
Abbreviations: VTE, venous thromboembolism; SD, standard deviation; CrCl, creatinine clearance; NSAIDs, nonsteroidal anti-inflammatory drugs; IQR, interquartile range.

a higher mortality rate (p < 0.001). Compared with VTE patients without cancer, those with GBM had a higher rate of PE recurrences (p < 0.01), major bleeding (p < 0.001), particularly extracranial hematoma (p < 0.001) and a higher mortality rate (p < 0.001).

4. Discussion

Treatment decisions in patients with GBM who develop VTE are often made on an empirical individual basis, including evaluating the expected morbidity and mortality associated with different treatment options. Our data, obtained from a large series of GBM patients with acute VTE, reveal that most of these patients received initial therapy at (slightly) lower than recommended doses of heparin and for a shorter period of time, thus suggesting that physicians may feel concerned about the risk of bleeding. Interestingly however, the rate of major bleeding was lower than it could have been expected, since only one out of 72 patients bled in the brain. Our rate of intracranial bleeding while on anticoagulant therapy (3.58 events per 100 patient-years)

Table 2
Treatment strategies in patients with glioblastoma, other cancers or no cancer.

	Glioblastoma	Other cancers	No cancer
Patients, N	72	11,811	41,663
Duration of anticoagulation			
Days (mean ± SD)	140 ± 145	211 ± 281*	271 ± 323‡
Days (median-IQR)	96 (39–183)	133 (86–236)*	185 (109–302)‡
Duration of follow-up			
Days (mean ± SD)	202 ± 251	299 ± 401†	392 ± 458‡
Days (median, IQR)	139 (54–278)	168 (92–355)	226 (129–441)†
Initial therapy			
Low-molecular-weight heparin	67 (93%)	10,676 (90%)	36,911 (89%)
Mean LMWH doses (IU/kg/day)	164 ± 48	175 ± 43*	179 ± 39*
Unfractionated heparin	3 (4.2%)	805 (6.8%)	3024 (7.3%)
Fondaparinux	1 (1.4%)	167 (1.4%)	866 (2.1%)
Rivaroxaban	0	21 (0.18%)	274 (0.66%)
Thrombolytics	1 (1.4%)	33 (0.28%)	267 (0.64%)
Inferior vena cava filter	6 (8.3%)	542 (4.6%)	805 (1.9%)†
Long-term therapy			
Vitamin K antagonists	9 (12%)	4426 (37%)‡	32,222 (77%)‡
Low-molecular-weight heparin	56 (78%)	6351 (54%)‡	7469 (18%)‡
Mean LMWH doses (IU/kg/day)	141 ± 46	151 ± 47	145 ± 49
Fondaparinux	1 (1.4%)	134 (1.1%)	223 (0.54%)
Rivaroxaban	0	52 (0.44%)	685 (1.6%)

Differences between patients with other cancers or without cancer versus those with glioblastoma: *p < 0.05; †p < 0.01; ‡p < 0.001.
Abbreviations: SD, standard deviation; IQR, interquartile range; LMWH, low-molecular-weight heparin; IU, international units.

Table 3
Clinical outcome during the course of anticoagulation in patients with glioblastoma, other cancers or no cancer.

	Glioblastoma		Other cancers		No cancer	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	72		11,811		41,663	
Recurrent PE	2	7.27 (1.22–24.0)	275	4.07 (3.61–4.57)	384	1.24 (1.12–1.37)†
Recurrent DVT	1	3.59 (0.18–17.7)	293	4.36 (3.88–4.88)	467	1.52 (1.38–1.66)
Major bleeding	4	14.5 (4.60–34.9)	574	8.49 (7.81–9.20)	971	3.14 (2.95–3.35)‡
Gastrointestinal	0	–	258	3.78 (3.34–4.26)	304	0.98 (0.87–1.09)
Intracranial	1	3.58 (0.18–17.7)	73	1.06 (0.84–1.33)	206	0.66 (0.58–0.76)
Hematoma	3	10.9 (2.76–29.5)	67	0.98 (0.76–1.23)†	238	0.76 (0.67–0.87)‡
Other	0	–	178	2.62 (2.26–3.03)	231	0.75 (0.65–0.85)
Death	34	122 (85.8–168)	3052	44.4 (42.9–46.0)‡	1962	6.28 (6.01–6.57)‡
Causes of death						
Pulmonary embolism	1	3.58 (0.18–17.7)	237	3.45 (3.03–3.91)	331	1.06 (0.95–1.18)
Initial PE	1	3.58 (0.18–17.7)	173	2.52 (2.16–2.91)	272	0.87 (0.77–0.98)
Recurrent PE	0	–	64	0.93 (0.72–1.18)	59	0.19 (0.15–0.24)
Sudden, unexpected	0	–	28	0.41 (0.28–0.58)	87	0.28 (0.22–0.34)
Bleeding	2	7.17 (1.20–23.7)	110	1.60 (1.32–1.92)	149	0.48 (0.41–0.56)‡
Cerebral	1	3.58 (0.18–17.7)	23	0.33 (0.22–0.49)	62	0.20 (0.15–0.25)
Gastrointestinal	0	–	54	0.79 (0.60–1.02)	44	0.14 (0.10–0.19)
Hematoma	1	3.58 (0.18–17.7)	3	0.04 (0.01–0.12)*	12	0.04 (0.02–0.07)*
Other	0	–	30	0.44 (0.30–0.62)	31	0.10 (0.07–0.14)
Disseminated cancer	23	82.4 (53.5–121)	1686	24.5 (23.4–25.7)‡	0	–
Unknown	4	14.3 (4.56–34.6)	358	5.21 (4.69–5.77)*	379	1.21 (1.10–1.34)‡
Other	3	10.8 (2.74–29.3)	465	6.77 (6.17–7.40)	779	2.50 (2.32–2.68)†

Differences between patients with other cancers or without cancer versus those with glioblastoma: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: IQR, interquartile range; PE, pulmonary embolism; DVT, deep vein thrombosis; CI, confidence intervals.

may seem unexpectedly low, but is similar to that reported in a series of 64 patients with GBM who developed VTE (only 36 were treated with anticoagulant therapy) [8], and in another RIETE study on 392 patients with acute VTE <60 days after neurosurgery [16]. Interestingly, there was a relatively low rate (8.3%) of vena cava filter insertion, although a recent RIETE study in 371 patients (of whom 60 with cancer) revealed that in VTE patients with a significant risk for bleeding, vena cava filter insertion was associated with a lower risk of PE-related mortality compared with anticoagulant therapy [14].

Overall, the rate of major bleeding during the course of anticoagulant therapy was similar to the rate of VTE recurrences both in patients with GBM (4 vs. 3 events, respectively) and in those with other cancers (574 vs. 568 events). However, the rate of fatal bleeds exceeded the rate of fatal VTE recurrences both in patients with GBM (two versus no deaths) and in those with other cancers (110 vs. 64 deaths). The higher risk of dying from bleeding than from recurrent VTE during the course of anticoagulation has been previously reported, and suggests that a less aggressive anticoagulant strategy (or a shorter duration) might reduce fatal bleeding with scarce influence on the rate of fatal PE [17]. These observations further support the development of properly designed studies addressed to evaluate optimal anticoagulation therapy in cancer patients with VTE.

The present study has a number of potential limitations. First, patients were not treated with a standardized anticoagulant regimen and treatment varied with local practice, which was influenced by a physician's assessment of a patient's risk of bleeding. Second, data from registries are susceptible to selection bias if a non-representative sample of patients is selected for analysis. However, the RIETE registry captured a broad range of cancer patients with acute symptomatic VTE from multiple medical centers, countries, and treatment settings, and the study cohort was less likely a skewed population. Third, to fulfill the definition of fatal PE in RIETE patients must first experience an objectively confirmed recurrent PE followed by death within 10 days. Thus, all sudden unexplained deaths, usually considered as "likely" fatal recurrent PE, and many patients dying of respiratory insufficiency are not considered in this analysis. Therefore, the rate of fatal PE may have been underestimated, especially after hospital discharge. However, some deaths occurring at home without diagnosis may also have been due to cerebral bleeding. Finally, the study did not use a central committee to assign cause of death, but the number of deaths in the registry renders this task virtually impossible. Fourth, the data reported from RIETE was entered into the registry by a variety of practitioners. This process may lend itself to inaccuracies in data reporting. Finally, the lack of data on the use of angiogenic inhibitors and other anticancer therapies in RIETE limits the quality of this study. It would be also interesting to know more details on the how many patients underwent a repeat CT scan of the brain after anticoagulant treatment was started and the proportion of those with small hematomas; if there were any changes in the neurological function. On the other hand, strengths of the current analysis include that a large number of consecutive unselected patients were enrolled, and that all VTE recurrences were objectively proven. The RIETE registry provides data on the treatment and outcome of VTE in a real-world situation with an unselected patient population (in contrast to the rigorously controlled conditions of randomized clinical studies) and its findings are hypothesis-generating.

In conclusion, this large prospective RIETE study showed that patients with GBM developing VTE had a similar outcome during the course of anticoagulant therapy than those with other cancers. Interestingly, the rate of major bleeding was similar. Only the mortality rate was higher.

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