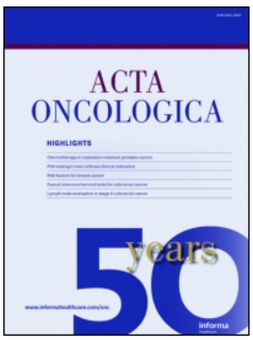

Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Thromboembolic events in brain tumour patients on bevacizumab

Gunjesh Kumar Singh , Nandini Menon , Monica Madhusing Jadhav , Rutuja Walavalkar , Hollis DSouza , Somnath Roy , Sudeep Das , Sujay Srinivas , Dilip Harindran Vallathol & Vijay M. Patil

To cite this article: Gunjesh Kumar Singh , Nandini Menon , Monica Madhusing Jadhav , Rutuja Walavalkar , Hollis DSouza , Somnath Roy , Sudeep Das , Sujay Srinivas , Dilip Harindran Vallathol & Vijay M. Patil (2020): Thromboembolic events in brain tumour patients on bevacizumab, Acta Oncologica, DOI: 10.1080/0284186X.2020.1815834

To link to this article: https://doi.org/10.1080/0284186X.2020.1815834

Published online: 08 Sep 2020.

ACTA ONCOLOGICA
https://doi.org/10.1080/0284186X.2020.1815834

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Thromboembolic events in brain tumour patients on bevacizumab

Gunjesh Kumar Singh*, Nandini Menon*, Monica Madhusing Jadhav, Rutuja Walavalkar, Hollis DSouza, Somnath Roy, Sudeep Das, Sujay Srinivas, Dilip Harindran Vallathol and Vijay M. Patil

Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India

ARTICLE HISTORY Received 26 May 2020; Accepted 21 August 2020

Background

Venous thromboembolism (VTE) is a frequently encountered phenomenon and is also seen in 1–2% of normal population [1]. However, it is a more common entity in post-operative period where impaired mobility leads to significant venous stasis. Apart from this, hypercoagulable state and injury to the endothelial lining are the two other proposed mechanisms responsible for its development [2,3]. Cancer patients are especially vulnerable to VTE and an increase in the level of tissue factor (pro-coagulant) is believed to be the possible explanation to this [4]. However, brain tumours deserve special mention due to the greater incidence of VTE in them. According to Stein et al. VTE was seen in 3.5% of all hospitalisations for brain tumour [5]. Similarly in another study by Smith et al. the incidence in this group was 19.4% [6]. Many authors have explored and proposed various factors that have link with its development. Sartori et al. suggested that the circulating tissue factor does not have a contributory role in causing VTE in all cancers, but in high-grade brain tumours, it certainly is one of the important precipitating factors [4]. Petterson et al. found age and sex to be the associated risk factors for VTE in this population [7]. Besides these, obesity, paresis, residual tumour, chemotherapy and anti vascular endothelial growth factor (VEGF) treatment have also been listed as significant predisposing factors [8]. Heenkenda et al. evaluated the role of genetic and non-genetic factors in causation of VTE among glioblastoma multiforme (GBM) patients and found B blood group to be a predictive risk factor [9].

Bevacizumab alone or in combination with chemotherapy has been approved by United States Food and Drug Administration (FDA) in recurrent and progressive GBM seeing the improved outcomes [10]. However, the European Medicines Agency (EMA) does not recommend its use and hence bevacizumab is the standard of care in these patients in the United States but not in Europe [11]. VTE is one of the most well known and dreaded side effects of this drug [12]. Khorana et al. worked in this direction, developed and validated a score to assess the risk of VTE, taking primary tumour site; pre-chemotherapy haemoglobin level, platelet counts, total leukocyte count (TLC) and body mass index (BMI) as components [13]. However, they couldn't draw any conclusion for brain tumour as a risk factor for VTE because of insufficient number of patients ($n = 4$).

To our belief, the use of bevacizumab in brain tumour patients does add to the risk of VTE in them. Hence, we conducted this study aiming to calculate the risk of VTE in this group of patients and its association with Khorana score.

Materials and method

Selection of patients

The primary brain tumour patients undergoing systemic therapy since 1st July 2015 in neuro-medical oncology unit of Tata Memorial Hospital, Mumbai, India, were included in this retrospective analysis. The eligibility criteria were:

1. Adult ambulatory patient aged $\geq$ 18 years
2. Relapsed or progressive GBM – WHO 2016 classification of brain tumours was used for the diagnosis. WHO 2007 classification was used for patients diagnosed before 2016.
3. Treated with bevacizumab
4. Time period – 1st July 2015 to 31th December 2018

The patients fulfilling the above mentioned inclusion criteria completely were selected and the data was entered in an excel sheet. The study methodology was approved by the Institutional Ethics Committee – III, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai – 410210, India. Waiver of consent was obtained. Principle of declaration of Good clinical practice (GCP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) were obtained. All patients had left written informed consent prior to chemotherapy.

Data collection

From the above mentioned data set, VTE events, the respective Khorana scores along with the demographic data were extracted and following were noted –

CONTACT Vijay M. Patil vijaypgi@gmail.com Department of Medical Oncology, Tata Memorial Hospital, Parel 400012, Mumbai, India
*Co-first authorship.

- Occurrence of VTE – Clinical suspicion (symptomatic) was confirmed by Doppler imaging or computed tomography angiogram. VTE occurrence during and 30 days after the last bevacizumab dose was taken into account.
- Concurrent use of chemotherapy and steroids
- Pre-bevacizumab haemoglobin level.
- Pre-bevacizumab platelets count
- Pre-bevacizumab TLC level
- BMI of the patient

Khorana score was calculated and patients were divided into 3 risk groups [13]. As per this scoring system, scores were allotted to pre-bevacizumab laboratory and clinical parameters: primary tumour site (score 1 or 2), haemoglobin leveL $<$ 100 g/L or red cell growth factor use (score-1); TLC $>11 \times 10^9$/L (score-1); platelet count $\geq 350 \times 10^9$/L (score-1); BMI $\geq$ 35 kg/m2 (score-1). As in our study, the primary tumour site was brain and Khorana score does not include this tumour as high risk, we used score 0 for the first category. All the scores were added to get a final score based on which the final risk stratification was done as:

1. Low risk – score 0
2. Intermediate risk – score 1 or 2
3. High risk – score $\geq$ 3

Treatment

All the patients with relapsed or progressive GBM were discussed in joint neuro-oncology meeting and asked for inclusion in the study. These patients were ineligible for re-surgery or re-irradiation and hence were offered bevacizumab either alone or in combination with chemotherapy. The choice of single agent therapy or combination was based on Eastern Cooperative Oncology Group Performance Status and the presence of co-morbidities. Bevacizumab was administered every 2–3 week. Each dose was given as per standard protocol. Premedication drugs like ondansetron (8 mg), dexamethasone (12 mg) and ranitidine (50 mg) were used $15-20$ min prior to bevacizumab. Bevacizumab in a dose of 10 mg/kg body weight was infused over 90 min in the first cycle and if tolerated well subsequent doses were administered in 60 min. The drug was continued either till disease progression or intolerable side effects. The drug was also stopped if financials of the patient were inadequate.

Statistical analysis

Statistical analysis was done *via* SPSS version 20 and R version 3.5.3. Descriptive analysis was performed. Pearson correlation analysis was done and the Pearson correlation coefficient was estimated between concurrent chemotherapy use, steroid use, Khorana score and risk of VTE. p-Value $\leq$.05 was considered significant.

Results

Baseline characteristics

Out of total 80 patients, 60 (75%) were males and 20 (25%) were females. 68 (85%) patients belonged to the younger and 12 (15%) belonged to the older (age $>$ 60 years) group. The median number of bevacizumab cycles given was 5 (range, 1–24) and median duration of follow up was 26 months (range, 1–37 months).

VTE during bevacizumab and assosciated factors

Out of the 80 patients included in the study; 7 (8.8%) had VTE events after starting bevacizumab. VTE was diagnosed in the form of deep vein thrombosis (DVT) in 4 (5%) and pulmonary thromboembolism (PTE) in 3 (3.8%) patients. Out of these 7 patients, 2 expired and the cause of death was believed to be PTE. 3 (42.8%) patients received concurrent chemotherapy with irinotecan while 1 (14.28%) received lomustine. All patients with VTE were given steroids (dexamethasone) during the course of treatment. We didn't find any significant association between VTE and the concurrent use of chemotherapy (Fisher exact test, p-value $=$ .387); meanwhile use of steroid was also not seen to influence the risk of VTE, (Fisher exact test, p-value $=$ .685).

Khorana score and its correlation with VTE

Of all, 43 (53.8%) patients belonged to the low risk category of Khorana score, 37 (46.2%) to the intermediate category and none to the high risk category. Table 1 mentions detailed Khorana scores. Out of 7 patients with VTE, 2 (28.57%) patients had Khorana score 0, 4 (57.14%) patients had score 1 and only 1(14.28%) patient had score 2 (Table 2). There was no significant association between Khorana scores obtained and VTE (fisher exact test, p-value $=$ .171).

Discussion

This retrospective study was conducted to find out the incidence of VTE in brain tumour patients undergoing anti VEGF therapy (bevacizumab). It was seen in 8.8% of the enrolled cases. We didn't find any significant association between VTE and the use of concurrent chemotherapy (Fisher exact test, p-value $=$ .387) and use of steroid was also not seen to increase the risk of VTE (Fisher exact test, p-value $=$ .685). Further, we also noted that most of our patients diagnosed with VTE belonged to either low risk or intermediate risk category and none belonged to the high risk one.

Yust-Katz et al. conducted a retrospective study of 440 GBM patients to see the prevalence of VTE and its association with the Khorana score. In contrast to our finding, they found a higher occurrence of VTE in there cohort, which was 22%. They also proposed that obesity, recurrent VTE, raised TLC and steroid use were the factors significantly associated with the development of VTE in GBM [14]. Also, they labelled Khorana score as a non-predictive tool for VTE diagnosis [14]. Similarly, in our study we also didn't find any relation

Table 1. Khorana score.

Parameters	Number	Percentage (%)
Pre-bevacizumab haemoglobin <10 g/dL or using RBC growth factors		
Yes	5	6.3
No	75	93.7
Pre-bevacizumab platelet count $\geq 350 \times 10^9$/L		
Yes	3	3.8
No	77	96.3
Pre- bevacizumab leukocyte count $>11 \times 10^9$/L		
Yes	09	11.3
No	71	88.7
Body mass index (BMI) ≥ 35 kg/m^2		
Yes	25	31.3
No	55	68.7
Khorana score		
0	43	53.8
1	33	41.3
2	4	5
3	0	0

Table 2. Khorana score and VTE.

	Venous thromboembolism (VTE)	
Khorana score	Yes	No
0	2 (4.7%)	41 (95.3%)
1	4 (12.1%)	29 (87.9%)
2	1 (25%)	3 (75%)
3	0	0

between khorana score and VTE. However, our results may be hypothesis-generating rather than definitive, due to the small number of patients included. Misch et al. carried out a retrospective study to see the rate of VTE in glioma patients receiving bevacizumab and found VTE in 13% of patients. They suggested that raised D-dimer levels and paresis were the factors impacting VTE [15]. Kuk et al. did a retrospective analysis to see VTE events in ovarian cancer patients receiving bevacizumab with or without chemotherapy and found that VTE was evident only in the patients on bevacizumab. They divided their patients into low, medium and high risk categories as per Khorana score. Out of 57 ovarian cancer patients, only 3 and 2 patients with high and medium risk respectively experienced VTE. None of the patients with low risk had VTE. They concluded that the use of bevacizumab was associated with a statistically non-significant increase in VTE risk in the high-risk group compared to the medium risk group [16].

Many studies have also discussed the role of VTE prophylaxis in brain tumour patients knowing the obvious risk. In this context, the role of anticoagulation therapy for prevention of VTE in patients with high grade glioma was explored in PRODIGE trial [17]. This therapy was seen to reduce VTE events however, it was not statistically significant. Also, due to the higher incidence of intracranial haemorrhage, the role of prophylactic anticoagulation therapy remains uncertain in these patients [17].

Patients with primary brain tumour have considerable risk of developing VTE and the use of bevacizumab further adds to the threat. However, the overall occurrence of VTE was lower in our cohort in comparison to other studies in the literature. Hence we suggest development and instillation of a VTE assessment tool for cancer patients in general and brain tumour patients in particular, which can aid in easy and timely recognition of the high risk cases so that prophylactic anticoagulant therapy can be initiated.

There are some limitations of our study. First is the retrospective nature of the study. Our hospital is a tertiary centre and majority of patients stay far and many come from other states, which may cause under reporting of VTE as many patients default and never report back. Hence a prospective study will take care of this issue and help in better understanding. Secondly, the total number of cases included in the analysis is small. Also, as only symptomatic or suspected VTE patients are selected for further evaluation and confirmation, the estimated rate of VTE gets compromised and may not be representative. Still, to the best of our knowledge, this is the first study from India attempting to find out the incidence of VTE in brain tumour patients on bevacizumab and hence is unique.

Conclusion

The incidence of VTE in primary brain tumour patients on bevacizumab therapy is low. Concurrent use of chemotherapy and steroids does not have an impact on the occurrence of VTE. Low and intermediate risk Khorana scores are unable to predict the risk of VTE in our population.

Ethical approval

The study methodology was approved by Institutional Ethics Committee – III, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai – 410210, India. Waiver of consent was obtained. Principle of declaration of Good clinical practice (GCP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was obtained. All patients gave informed written consent before participation.

Disclosure statement

The authors declare that they have no competing interests.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

References

[1] Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. Eur J Vasc Endovasc Surg. 2003;25(1):1–5.

[2] Wakefield TW, Myers DD, Henke PK. Mechanisms of venous thrombosis and resolution. Arterioscler Thromb Vasc Biol. 2008; 28(3):387–391.

[3] Saha P, Humphries J, Modarai B, et al. Leukocytes and the natural history of deep vein thrombosis: current concepts and future directions. Arterioscler Thromb Vasc Biol. 2011;31(3):506–512.

[4] Sartori MT, Della Puppa A, Ballin A, et al. Prothrombotic state in glioblastoma multiforme: an evaluation of the procoagulant activity of circulating microparticles. J Neurooncol. 2011;104(1):225–231.

[5] Stein PD, Beemath A, Meyers FA, et al. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119(1):60–68.

[6] Smith TR, Nanney AD, 3rd, Lall RR, et al. Development of venous thromboembolism (VTE) in patients undergoing surgery for brain tumors: results from a single center over a 10 year period. J Clin Neurosci. 2015;22(3):519–525.

[7] Petterson TM, Marks RS, Ashrani AA, et al. Risk of site-specific cancer in incident venous thromboembolism: a population-based study. Thromb Res. 2015;135(3):472–478.

[8] Perry JR. Thromboembolic disease in patients with high-grade glioma. Neuro-oncology. 2012;14(Suppl 4):iv73–80.

[9] Heenkenda MK, Malmström A, Lysiak M, et al. Assessment of genetic and non-genetic risk factors for venous thromboembolism in glioblastoma – the predictive significance of B blood group. Thromb Res. 2019;183:136–142.

[10] Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733–4740.

[11] Gil-Gil MJ, Mesia C, Rey M, et al. Bevacizumab for the treatment of glioblastoma. Clin Med Insights Oncol. 2013;7:123–135.

[12] Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA. 2008;300(19): 2277–2285.

[13] Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902–4907.

[14] Yust-Katz S, Mandel JJ, Wu J, et al. Venous thromboembolism (VTE) and glioblastoma. J Neurooncol. 2015;124(1):87–94.

[15] Misch M, Czabanka M, Dengler J, et al. D-dimer elevation and paresis predict thromboembolic events during bevacizumab therapy for recurrent malignant glioma. Anticancer Res. 2013;33(5): 2093–2098.

[16] Kuk A, Magnowska M, Suchy W, et al. Retrospective evaluation of thromboembolism risk in ovarian cancer patients treated with bevacizumab. Target Oncol. 2017;12(4):495–503.

[17] Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost. 2010;8(9): 1959–1965.