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ORIGINAL ARTICLE

Predictors of Venous Thromboembolism in Patients with Glioblastoma

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Abstract To evaluate different risk factors associated with development of venous thromboembolism (VTE) in patients with Glioblastoma (GBM). A retrospective chart review was performed to include patients diagnosed with GBM from 2001 to 2011. Cases (n = 162) were defined as patients with GBM who developed VTE after diagnosis of GBM. Controls (n = 840) were defined as patients with GBM with no history of VTE. Data was collected for multiple variables including age, gender, race, length of hospital stay after brain biopsy, total number of hospital admissions unrelated to VTE, Karnofsky Performance Status (KPS), use of Bevacizumab and any bleeding episodes. Patients with GBM who had VTE had poorer KPS scores, with the majority (57 %) being in between 40 and 70, as compared to the controls where majority (82 %) had better performance (KPS 80-100). For every one year increase in age, the odds of developing VTE increased by 3 % (OR 1.03, 95%CI 1.02-1.04, $p < 0.001$) with the mean age being 61.8 ± 11.4 years. GBM patients who developed a VTE were found to have greater number of hospital admissions (OR 1.43, 95%CI 1.33-1.53, $p < 0.001$) and longer stays in hospital after GBM biopsy (OR 1.14, 95%CI 1.09-1.18, $p < 0.001$). Patients receiving Bevacizumab were more likely to develop VTE (OR 1.79, 95%CI 1.21-2.64, $p < 0.001$) and were more likely to have a bleed (OR 3.78, 95 % CI 2.70-5.30, $p < 0.001$). Patients with GBM are at a higher risk of developing VTE. The risk is higher in older patients who require multiple hospital admissions, longer duration of hospital stays related to GBM biopsy, and in patients with lower KPS scores. Bevacizumab use is related to a higher incidence of VTE as well as bleeds. This study suggests that a more aggressive strategy for VTE prophylaxis should be considered in GBM patients with risk factors for VTE.

Keywords GBM · Venous thromboembolism · KPS scale · Bevacizumab

Introduction

Ever since the first descriptions of an association of malignancy and thrombosis by Bouillaud and Trousseau in the nineteenth century, multiple studies have been conducted to determine the incidence, strength of association, pathogenesis, risk factors and therapeutic modalities of this association [1]. Brain tumors, especially Glioblastoma (GBM), have classically been linked to the development of deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE), which adds greatly to the morbidity and mortality associated with this catastrophic malignancy [2]. Multiple mechanisms have been proposed to explain this association. These include chronic activation of the coagulation system by local and circulating procoagulants, such as tissue factor and tissue factor containing microparticles (released into circulation by the tumor) respectively [3]. Additionally, immobility related to

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GBM further adds to the inherent capacity of these tumors to increase the risk of VTE.

Review of literature shows limited data on predictors of venous thromboembolism (VTE) in patients with GBM. There is limited data regarding predictive model for VTE development in other types of cancers [4, 5]. The purpose of this study was to determine possible risk factors that could lead to the development of VTE in this patient population. The risk factors analyzed in this study included age, sex, race, age at diagnosis of GBM and VTE, Karnofsky Performance Status (KPS) scores, number of hospital admissions and duration of hospital stay related to GBM biopsy.

Materials and Methods

The study was approved by the institutional review board (IRB# 9082). A retrospective chart review was performed to include patients diagnosed with GBM from years 2001 to 2011. The total patient population was 1002. Cases (n = 162) were defined as patients with GBM who developed symptomatic VTE (DVT, PE or both) after diagnosis of GBM. Controls (n = 840) were defined as patients with GBM with no history of VTE. The method of diagnosis was venous duplex for DVT and CT angiogram or V/Q scan for pulmonary embolism.

Data was collected for multiple variables including age at time of diagnosis of GBM and VTE, gender, race, length of hospital stay after brain biopsy, total number of hospital admissions, KPS, use of bevacizumab and any bleeding episodes. Length of hospital stay after brain biopsy was defined as the total number of days from admission date until the discharge date. The total number of hospital admissions included all admissions after the diagnosis of GBM, other than the admissions related to development of VTE.

The KPS score was analyzed immediately after GBM biopsy, but before VTE development. In most cases, it was based on the documentation of the oncologist or neurosurgeon. If the KPS score of a patient was not documented in the visits, it was calculated based on other types of documentation recorded by different physicians such as physical examination, the level of physical activity of the patient, their ability to carry out household chores, whether or not the patient required physical rehabilitation, etc.

Statistical Analysis

Univariate comparisons between cases and controls were performed using a two-group independent t-test for age and using chi-square tests for the categorical variables. In order to

Table 1 Characteristics of patients along with univariate and multivariate analysis

Factors		All (N = 1002)	Cases (N = 162)	Controls (N = 840)	Univariate Analysis		Multivariate Analysis	
					OR (95 % CI)	*P* Value	OR (95 % CI)	*P* Value
Age	Mean ± SD	57.2 ± 14.1	61.8 ± 11.4	56.3 ± 14.5	1.03 (1.02, 1.04)	<0.001		
Gender	Male	590 (59 %)	92 (57 %)	498 (59 %)	0.90 (0.64, 1.27)	0.555		
	Female	412 (41 %)	70 (43 %)	342 (41 %)				
Race	Caucasian	631 (63 %)	121 (75 %)	510 (61 %)	1.38 (0.78, 2.43)	0.002		
	AA[1]	262 (26 %)	25 (15 %)	237 (28 %)	0.61 (0.31, 1.20)			
	Other	109 (11 %)	16 (10 %)	93 (11 %)				
Length of stay (in days)	Mean ± SD	4.2 ± 4.0	6.3 ± 5.7	3.8 ± 3.4	1.14 (1.09, 1.18)	<0.001		
KPS	80–100	724 (72 %)	35 (22 %)	689 (82 %)	0.04 (0.02,0.07)	<0.001	0.04 (0.02, 0.08)	<0.001
	40–70	217 (22 %)	93 (57 %)	124 (15 %)	0.60 (0.34, 1.06)		0.62 (0.34, 1.10)	
	0–30	61 (6 %)	34 (21 %)	27 (3 %)				
Number of Admissions	Mean ± SD	2.9 ± 2.7	5.3 ± 4.1	2.4 ± 2.1	1.4 (1.33, 1.53)	<0.001		
Biopsy to VTE (days)	Mean ± SD	N/A	78.3 ± 84.9	N/A				
Anticoagulation to Bleed (days)	Mean ± SD	N/A	111.8 ± 136.3	N/A				
Bleed	None	769 (77 %)	97 (60 %)	672 (80 %)		<0.001	1.96 (1.27, 3.02)	0.002
	GI[2]	51 (5 %)	20 (12 %)	31 (4 %)	4.47 (2.45,8.15)			
	GU[3]	6 (1 %)	2 (1 %)	4 (<1 %)	3.46 (0.63, 19.17)			
	Intracranial	170 (17 %)	40 (25 %)	130 (15 %)	2.13 (1.41, 3.22)			
	OMF[4]	6 (1 %)	3 (2 %)	3 (<1 %)	6.93 (1.38, 34.82)			
Bevacizumab Use	No	813 (81 %)	118 (73 %)	695 (83 %)	1.79 (1.21, 2.64)	0.004	1.75 (1.07, 2.85)	0.025
	Yes	189 (19 %)	44 (27)	145 (17 %)				

[1] African Americans, [2] Gastrointestinal, [3] Genitourinary, [4] Oro-maxillo-facial

Table 2 Descriptive statistics of patients with venous thromboembolism (VTE)

Factor	N (%)
Venous Thromboembolism (VTE)	
Deep Vein Thrombosis (DVT)	61 (38)
Pulmonary Embolism (PE)	91 (56)
Both DVT and PE	10 (6)
Duration of Anticoagulation	
None[1]	60 (37)
0–6 months	47 (29)
6–12 months	17 (10)
> 12 months	37 (23)
Inferior vena cava filter placed	
No	89 (55)
Yes	73 (45)

[1] Anticoagulation refused by the patient or stopped after a major bleeding episode or due to a contraindication

Table 3 Bevacizumab use and its association with different types of bleeds

Type of bleed	Bevacizumab used (N = 189)	Bevacizumab not used (N = 813)	*P*-value
Gastrointestinal	26 (14 %)	25 (3 %)	<0.001
Genitourinary	2 (1 %)	4 (0.5 %)	
Intracranial	45 (30 %)	114 (14 %)	
Oro-maxillo-facial	2 (1 %)	4 (0.5 %)	

identify possible independent predictors of VTE, a multiple logistic regression model was constructed using GBM status as the dependent variable and initially all variables with a univariate *p*-value of <0.2 as independent variables. Variables were reduced in a manual stepwise manner to arrive at a final model. Statistical significance was set at $p < 0.05$. All analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 1002 patients were analyzed in this study. Of these, 590(59 %) were males and 412(41 %) were females. The most common race was Caucasian, comprising 631 (63 %) patients, followed by African American with 262 (26 %) patients. The remaining 109 (11 %) patients comprised all other races. The mean age was 61.8 ± 11.4 years in cases and 56.3 ± 14.5 years in the controls (odds ratio [OR] 1.03, 95 % CI 1.02-1.04, $p < 0.001$) (Table 1). For every one year increase in age, the odds of developing VTE increased by 3 % (OR 1.03, 95%CI 1.02-1.04, $p < 0.001$) with the mean age being 61.8 ± 11.4 years.

The mean duration of VTE development from time of brain biopsy was 78.3 ± 84.9 days. In patients who developed VTE ($n = 162$), 73 (45 %) received an inferior vena cava filter. The main reasons for IVC filter placement were either a major contraindication of anticoagulation or an episode of a major bleed. Of the remaining 89 patients, 60 (37 %) received no anticoagulation (either due to patients' refusal or due to an episode of major bleed), 48 (30 %) received anticoagulation for less than 6 months, 17 (10 %) received anticoagulation for 6 to 12 months and 37 (23 %) received anticoagulation for more than 12 months (Table 2).

Patients with GBM who had VTE had poorer KPS scores. The majority (57 %) were between 40 and 70, as compared to the controls where the majority (82 %) had a better performance status (KPS 80-100). This difference was found to be statistically significant ($p < 0.001$) (Fig. 1 and Table 2).

GBM patients who developed a VTE were found to have more admissions when compared to the controls. The average number of admissions for cases was 5.3 ± 4.1 and for controls it was 2.4 ± 2.1. This difference was found to be statistically significant (OR 1.43, 95%CI 1.33-1.53, $p < 0.001$). In

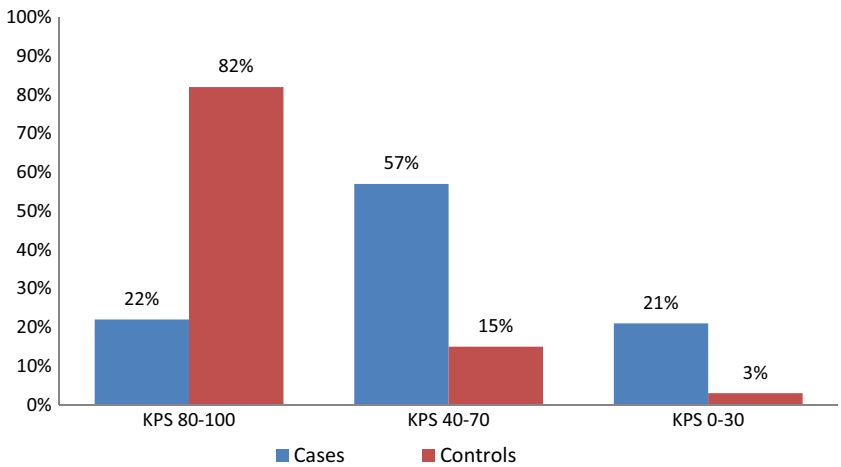

Fig. 1 Distribution of cases and controls based on KPS scores

Table 4 Bevacizumab and its association with bleeding after bleeding is used as a binary variable

Bleed	Bevacizumab used (N = 189)	Bevacizumab not used (N = 813)	OR (95 % CI)	*P*-value
Yes	86 (46 %)	147 (18 %)	3.78 (2.70, 5.30)	<0.001
No	103 (55 %)	666 (82 %)		

addition, development of VTE was also related to longer hospital stays after biopsy related to GBM (OR 1.14, 95%CI 1.09-1.18, $p < 0.001$) and more deaths (OR 4.53, 95%CI 3.01-6.80, $p < 0.001$).

Patients receiving bevacizumab were more likely to develop VTE (OR 1.79, 95%CI 1.21-2.64, $p > 0.001$) and were more likely to have a bleed (OR 3.78, 95 % CI 2.70-5.30, $p < 0.001$) when compared to patients not receiving bevacizumab (Tables 3 and 4). The common sites of bleeding were gastrointestinal, genitourinary, intracranial and oro-maxillo-facial. The most common site of bleeding in both cases and controls were intracranial (25 % of the cases vs. 15 % of the controls) (Table 1 and Fig. 2).

Discussion

Semrad et al. concluded in their large retrospective study involving 9489 patients that VTE in malignant glioma is associated with increased mortality within 2 years (hazard ratio 1.3, CI 1.2-1.4) [6]. Chaichana et al. reported that 3 % of the patients who undergo craniotomy for tumor surgery develop VTE, with increased rates in older patients and those with hypertension, motor deficits and poor preoperative clinical conditions [7].The grade of the tumor is also directly proportional to the risk of VTE [8].

The incidence of VTE in high-grade glioma is astonishingly high, ranging between 20 %-30 %. These patients are at high risk of developing this complication throughout the course of the malignancy, with the peak number of cases reported in the immediate postoperative period (hazard ratio for developing VTE is 1.7 [95%CI 1.3–2.3] within 61 days after neurosurgery) [6, 9]. Risk factors include hypertension, old age, motor deficits and a poor preoperative clinical condition. Neurosurgery itself is not the primary culprit of increased VTE risk in such patients. Patients with cancer undergoing neurosurgery are 3 times more prone to have a fatal pulmonary embolism than patients without cancer undergoing similar surgeries [10, 11]. This raises curiosity over the unique biological characteristics of this tumor that makes the patient thrombogenic [9, 12].

The main aim of our study was to identify an association between different variables and the development of VTE in patients with GBM. We found that patients with GBM who developed a VTE were more likely to be older (mean age 61.8 ± 11.4 years); for every 1 year increase in age, the odds of developing VTE increased by 3 % (OR 1.03, 95%CI 1.02-1.04, $p < 0.001$). The frequency of hospital admissions as well as the duration of the hospital stay was significantly higher in the cases of VTE as compared to the controls. More deaths (OR 4.53, 95%CI 3.01-6.80, $p < 0.001$) were noted in the cases, which signifies the additive detrimental effects of VTE on the already unfavorable prognosis of GBM.

First line treatment for primary GBM is maximal surgical resection and chemoradiotherapy with temozolomide, followed by maintenance with temozolomide (with or without radiotherapy) [13, 14]. Despite this, the median survival for these patients is approximately 15 months, making it one of the most lethal malignancies [15]. In 2009, the U.S. Food and Drug Administration approved bevacizumab for GBM as a single agent for patients with progressive disease following prior therapy [16] based on the results of two phase II trials [17, 18]. Regarding its use in the first line treatment of GBM, 2 phase III randomized-controlled clinical trials failed to show any survival benefit, but both demonstrated 3–4 months

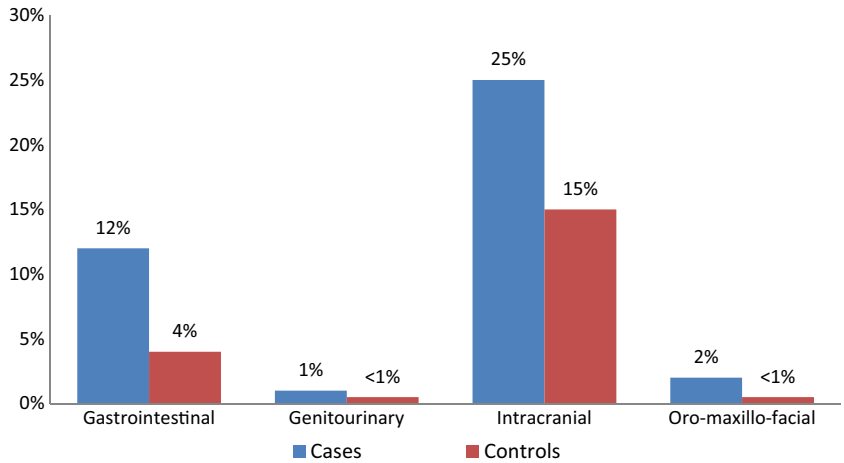

Fig. 2 Comparison of types of bleeding episodes between cases and control

improvement in progression-free survival [19, 20]. The risk of VTE is higher with bevacizumab, especially if bevacizumab is used along with chemoradiotherapy (7.46 %) rather than as a single agent (4.27 %) [21].

In our study, 27 % (n = 44) of the cases were also treated with bevacizumab as compared to only 17 % (n = 145) in the controls. Our study concluded that patients receiving bevacizumab were more likely to have a bleed as compared to patients not receiving bevacizumab, with the majority of the episodes being intracranial (30 %). In a meta-analysis of 20 randomized controlled trials, bevacizumab was associated with a high incidence of all-grade hemorrhage [30.4 % (95 % CI 21.5-40.9), with 3.5 % (95 % CI 2.2-5.7 %) being high grade (grade 3–5)] [22].

Bevacizumab has been classically linked to the development of arterial and venous thromboembolism (Relative risk of 1.3) [23]. Our study showed a higher incidence of VTE development with use of bevacizumab (OR 1.79, 95%CI 1.21-2.64, $p > 0.001$). Using a drug which is thrombogenic in a patient already at an increased risk of VTE has been confusing for the physicians. This necessitates the use of anticoagulants in these patients if they do develop VTE. But as gliomas are inherently prone to bleeding, clinicians have been reluctant to use anticoagulants in such patients. Traditionally, they have been more inclined towards inferior vena cava filters rather than opting for anticoagulation, which is another area of debate. In fact, administering anticoagulants to such patients puts them at a 2 % higher risk of developing a tumoral bleed [24]. In our patient population, 45 % (n = 73) of the cases underwent inferior vena cava filter placement for the prevention of pulmonary embolisms, while 55 % (n = 89) were put on anticoagulation, the duration of which varied from 3 months to more than 12 months. Ideally, most patients diagnosed with GBM should receive bevacizumab for better outcomes, however, in case of an episode of VTE or a major bleed, options include dose reduction or stopping bevacizumab completely, depending upon the severity of the bleed or size of VTE. Bevacizumab use should be under strict monitoring parameters. As this drug increases risk of VTE (as well as bleeding), clinicians should keep a close eye on early signs and symptoms of VTE in patients using bevacizumab. Additionally, patients taking this medication should be advised to maintain adequate mobility to reduce their risk of VTE.

The main limitation of this study is that it is a single center, retrospective study and the results might not be applicable to the general population. Another weakness of this study is the determination of KPS scores. For patients with no documentation of KPS score, they were calculated based on factors such as physical examination, the level of physical activity of the patient, their ability to carry out household chores, whether or not the patient required physical rehabilitation etc. Such a determination can result in researcher bias. However, majority of the patients had KPS scores documented in their charts (as it is commonly used among neurosurgeons and oncologists to assess and follow patient's clinical status). For patients without documentation of KPS scores, all efforts were made to determine the KPS scores based on detailed chart analysis in a clear manner.

Our study found significant associations between different variables and the development of VTE in patients with GBM, but a causal relationship cannot be ascertained. We suggest that a well-designed prospective study be conducted that might address this issue to better understand the risk factors involved in its pathogenesis. Efforts should be made to 'predict' the risk of VTE in glioma patients to avoid complications. Benefits of bevacizumab use should be assessed and weighed against the devastating vascular complications it incurs. Taking into account the results of this study, prospective studies should evaluate the possibility of prophylactic anticoagulation in high risk patients with GBM. Such studies can help guide the clinicians in managing this patient population with a more robust approach.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

TM has been an advisor to Roche Genentech.

Ethical Approval The study was approved by the institutional review board (IRB# 9082).

References

1. Thaler J, Ay C, Kaider A, Reitter EM, Haselbock J, Mannhalter C, Zielinski C, Marosi C, Pabinger I (2014) Biomarkers predictive of venous thromboembolism in patients with newly diagnosed high-grade gliomas. Neuro-Oncology 16(12):1645–1651. doi:10.1093/neuonc/nou106
2. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 5(3):632–634. doi:10.1111/j.1538-7836.2007.02374.x
3. Magnus N, D'Asti E, Garnier D, Meehan B, Rak J (2013) Brain neoplasms and coagulation. Semin Thromb Hemost 39(8):881–895. doi:10.1055/s-0033-1357483
4. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111(10):4902–4907. doi:10.1182/blood-2007-10-116327
5. Connolly GC, Khorana AA, Kuderer NM, Culakova E, Francis CW, Lyman GH (2010) Leukocytosis, thrombosis and early mortality in cancer patients initiating chemotherapy. Thromb Res 126(2):113–118. doi:10.1016/j.thromres.2010.05.012
6. Semrad TJ, O'Donnell R, Wun T, Chew H, Harvey D, Zhou H, White RH (2007) Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg 106(4):601–608. doi:10.3171/jns.2007.106.4.601

7. Chaichana KL, Pendleton C, Jackson C, Martinez-Gutierrez JC, Diaz-Stransky A, Aguayo J, Olivi A, Weingart J, Gallia G, Lim M, Brem H, Quinones-Hinojosa A (2013) Deep venous thrombosis and pulmonary embolisms in adult patients undergoing craniotomy for brain tumors. Neurol Res 35(2):206–211. doi:10.1179/1743132812Y.0000000126
8. Seidel C, Hentschel B, Simon M, Schnell O, Heese O, Tatagiba M, Krex D, Reithmeier T, Kowoll A, Weller M, Wick W (2013) A comprehensive analysis of vascular complications in 3,889 glioma patients from the German glioma network. J Neurol 260(3):847–855. doi:10.1007/s00415-012-6718-9
9. Jenkins EO, Schiff D, Mackman N, Key NS (2010) Venous thromboembolism in malignant gliomas. J Thromb Haemost 8(2):221–227. doi:10.1111/j.1538-7836.2009.03690.x
10. Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MN, Liebman H, Mendelson D, Raskob G, Somerfield MR, Thodiyil P, Trent D, Francis CW, American Society of Clinical O (2007) American society of clinical oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol : Off J Am Soc Clin Oncol 25(34):5490–5505. doi:10.1200/JCO.2007.14.1283
11. Gallus AS (1997) Prevention of post-operative deep leg vein thrombosis in patients with cancer. Thromb Haemost 78(1):126–132
12. Sartori MT, Della Puppa A, Ballin A, Campello E, Radu CM, Saggiorato G, d'Avella D, Scienza R, Cella G, Simioni P (2013) Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: a potential prothrombotic role. Thromb Haemost 110(2):378–385. doi:10.1160/TH12-12-0957
13. Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, Hahn WC, Ligon KL, Louis DN, Brennan C, Chin L, DePinho RA, Cavenee WK (2007) Malignant astrocytic glioma: genetics, biology, and paths to treatment. Genes Dev 21(21):2683–2710. doi:10.1101/gad.1596707
14. Sathornsumetee S, Reardon DA, Desjardins A, Quinn JA, Vredenburgh JJ, Rich JN (2007) Molecularly targeted therapy for malignant glioma. Cancer 110(1):13–24. doi:10.1002/cncr.22741
15. Fine HA (2014) Bevacizumab in glioblastoma–still much to learn. N Engl J Med 370(8):764–765. doi:10.1056/NEJMe1313309
16. Koukourakis GV (2012) Has bevacizumab (avastin) given extra therapeutic gain in metastatic colorectal cancer and malignant brain gliomas? Systematic review answering this question. Recent Patents Inflamm Allergy Drug Discov 6(1):70–77
17. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS, Fine HA (2009) Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol : Off J Am Soc Clin Oncol 27(5):740–745. doi:10.1200/JCO.2008.16.3055
18. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T (2009) Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol : Off J Am Soc Clin Oncol 27(28):4733–4740. doi:10.1200/JCO.2008.19.8721
19. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran Jr WJ, Mehta MP (2014) A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370(8):699–708. doi:10.1056/NEJMoa1308573
20. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L, Cloughesy T (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370(8):709–722. doi:10.1056/NEJMoa1308345
21. Simonetti G, Trevisan E, Silvani A, Gaviani P, Botturi A, Lamperti E, Beecher D, Bertero L, Bosa C, Salmaggi A (2014) Safety of bevacizumab in patients with malignant gliomas: a systematic review. Neurol Sci 35(1):83–89. doi:10.1007/s10072-013-1583-6
22. Hapani S, Sher A, Chu D, Wu S (2010) Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology 79(1–2):27–38. doi:10.1159/000314980
23. Narita Y (2013) Drug review: safety and efficacy of bevacizumab for glioblastoma and other brain tumors. Jpn J Clin Oncol 43(6):587–595. doi:10.1093/jjco/hyt051
24. Wen PY, Schiff D, Kesari S, Drappatz J, Gigas DC, Doherty L (2006) Medical management of patients with brain tumors. J Neuro-Oncol 80(3):313–332. doi:10.1007/s11060-006-9193-2