Safety of bevacizumab in patients with malignant gliomas: A systematic review

Safety of bevacizumab with or without anticoagulant treatment in neuro oncological patients: a systematic review.

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Abstract

Introduction: neoangiogenesis has recently become a major target for the development of new antineoplastic drugs. The most serious adverse events linked to angiogenesis inhibitors are venous or arterial thromboembolism and hemorrhage. Thus, there is a need to define with more certainty the impact of these new drugs in terms of adverse effects in neurological patients.

Objective: to assess the risk of venous thromboembolism and bleeding in neuro-oncological patients treated with bevacizumab with or without concomitant anticoagulant therapy.

Material and methods: a review of the literature published since 2005 was performed in Medline, from which we identified 476 records. We assessed for eligibility 27 full text articles including retrospective analyses, retrospective reviews, and open label trials. The investigated drugs included bevacizumab alone, bevacizumab plus chemotherapy with or without concomitant radiation therapy, while only two articles dealt with Bevacizumab in association with anticoagulant treatment.

Results: a total of 2208 patients with brain tumor were identified and included in the analysis. Data confirmed that patients receiving bevacizumab had a major risk of developing thromboembolic events that increased progressively in association with radiotherapy and chemotherapeutic agents (4.27% vs 7,46%). Regarding bleeding, data showed that patients treated with anticoagulant had a significantly increased risk of severe intracranial bleeding (grades 3,4,5) compared to patients not receiving anticoagulant therapy (0.6% vs 8.2%).

Conclusion: The use of bevacizumab combined with chemo and radiotherapy is associated with a higher risk for venous thromboembolism compared to patients receiving antiangiogenic therapy alone. The associated use of anticoagulants and Bevacizumab far increases the risk of developing an intra-extracranial bleeding, higher than grade 3, compared to patients receiving Bevacizumab alone.

Keywords: brain tumor, bevacizumab, anti-VEGF, DVT, hemorrhage

Introduction

The prognosis of patients with glioblastoma remains poor despite considerable therapeutic progress in neuro-oncology: the overall median survival for patients treated with the current standard chemoradiotherapy regimen is approximately 15 months (Stupp R, N Engl J Med 2005; Stupp R, Lancet Oncol 2009; Wen and Kesari, New Eng J Med 2008). In selected patients populations within recent clinical phase II trials the median overall survival ranges from 19 to 22 months, probably due to improvement in supportive care and more aggressive salvage therapy. Even with current standard of care (concomitant chemo-radiotherapy followed by adjuvant chemotherapy with temozolomide) for newly diagnosed glioblastoma, the majority of patients recur within a year. Available salvage therapies at recurrence are modestly effective, and no single treatment can be considered the standard of care.

Angiogenesis has emerged as an attractive therapeutic target for therapy (Gagner, Brain Pathol 2005; Tuettenberg, Crit Rev Oncol Hematol, 2006), and inibition of VEGF (vascular endothelial growth factor)-mediated signaling has recently received considerable attention in the targeting of recurrent malignant gliomas. Angiogenesis is a physiological process that allows the formation of new blood vessels from preexisting vessels that occurs during embryonic and after birth to contribute to organ growth (Carmeliet, Nature 2000). In adulthood, angiogenesis occurs in the cycling ovary, in the placenta during pregnancy, in wound healing, and in response to physiological stimuli such as hypoxia and inflammation. Angiogenesis is a key factor in the growth of many human cancers (Hanahan D, Cell 2000; 100: 57-70), including brain tumors. High-grade gliomas, expecially glioblastomas, are particularly vascularized and are characterized hisologically by neovascularization, and overexpression of VEGF (Kargiotis, J Neuro-Oncol 2006; Norden, Neurology 2008). Bevacizumab, a humanized monoclonal antibody against circulating VEGF-A, has demonstrated promising radiological response rates (37.8-70.6%) when used alone or in combination with irinotecan in recurrent GBM (Vredenburgh, Clin Cancer Res 2007; Friedman et al, J Clin Oncol 2009; Zuniga, J Neurooncol 2009). Other reported benefits are a decreased need for corticosteroids in 33-72.7% of patients (Batchelor, Cancer Cell 2007; Norden, Neurology 2008; Vredenburgh, Oncologist 2010), and temporary improvement in neurological functions (Vredenburgh, Clin Cancer Res 2007), although the survival data were less impressive with PFS6 in 25-50% of the patients (Raizer 2010; Friedman 2009). Bevacizumab is generally well tolerated with an acceptable safety profile, although rare and potentially life-

threatening adverse events have been identified. The most common side effects are hypertension, fatigue, proteinuria, and poor wound healing (Armstrong, Neuro-Oncol 2012), but also other potentially more serious adverse events like venous and arterial thromboembolism, intracranial and extracranial hemorrhage, gastrointestinal perforation, and reversible posterior leukoencephalopathy are reported.

We reviewed the available published data to investigate the relationship between the use of bevacizumab and thromboembolic events (VTE), central nervous system (CNS) haemorrhage and extracranial bleeding in neuro oncological patients with or without concomitant anticoagulant therapy.

Material and methods

We reviewed the scientific literature to assess whether there was a significant increase in thromboembolism events and major bleeding events in patients with brain tumors receiving anti-VEGF therapies. A Medline research was performed including articlesn published since January 2005 up to July 2011. The search strategy combined terms for brain tumours/neoplasms and angiogenesis inhibitors to identify relevant information. Only studies which considered neuro-oncological patients treated with either bevacizumab alone or combined with radio-chemotherapy, with or without anticoagulants, were considered for the analysis.

Two authors indipendently evaluated 476 records. The 27 full text articles found were assessed for eligibility, which included retrospective analysis, retrospective reviews, and open label trials. Only two studies dealt with bevacizumab use and anticoagulants (Nghiemphu, 2008; Norden, 2011). We considered only articles reporting safety data.

Data were extracted independently by three authors using a pre-determined form. Quality was assessed using standardized criteria evaluating methodological quality (external validity, risk of bias according to Cochrane criteria, patient population features, outcome, follow up, drop out, randomization, blinding). Data about type of antiangiogenic drug, incidence of venous/arterial thromboembolism, and of haemorrhage were extrapolated too. Disagreements on extractions were resolved by discussion.

We analized the quality of included studies and the incidence of DVT/PE and hemorrhage for antiangiogenic therapy alone, combined with other chemotherapy or with chemo and radiotherapy.

We reported all thromboembolic events and hemorrhages, and evaluating the severity according to Common Terminology Criteria for Adverse Event (CTCAE) version 3.0. We defined as serious events any event of grade 3 or greater. Data have been separated to obtain the absolute number of thromboembolic events and bleedings in patients treated with bevacizumab alone, bevacizumab combined with chemotherapy, and bevacizumab used during concomitant chemo-radiotherapy.

To evaluate the association between treatment with bevacizumab alone or bevacizumab plus chemotherapy or bevacizumab plus chemo-radiotherapy and serious thromboembolic or bleeding events we used the chi-square text. We also evaluated the association between bevacizumab (alone or with other antineoplastic treatments) used with and without anticoagulants and serious bleeding events using the chi-square text with Yates' correction.

Results

We identified 27 full text articles reporting the use of bevacizumab in neuro-oncological patients. Bevacizumab alone was used in 2 studies (Chamberlein, 2009; Raizer, 2010), combined with other drugs in 20 studies in recurrent GBM (Vredenburgh, 2007; Nghiemphu, 2008; Norden, 2008; Bokstein, 2008; Kang, 2008; Friedman, 2009; Socinski, 2009; Taillibert, 2009; Zuniga, 2009; Poulsen, 2009; Bartolomeo, 2010; Thompson, 2010; Hasselbach, 2010; Verhoeff, 2010; Scott, 2010; Sathornsumetee, 2010; Francesconi, 2010; Reardon, 2011; Hofer, 2011; Fraum, 2011), combined with radio-chemotherapy in 4 studies in newly diagnosed GBM (Lai, 2008; Vredenburgh, 2010; Lai, 2011; Vredenburgh, 2011), and in 1 in recurrent HGG (Niyazi, 2010). In two studies bevacizumab was associated with anticoagulants included warfarin, low molecular weight heparin (LMWH) and fondaparinux. (Nghiemphu, 2008; Norden, 2011).

A total of 2208 patients with brain tumors were analyzed to investigate the relationship between the use of bevacizumab and thromboembolic events and bleedings.

Thromboembolic events ≥ grade 3 including deep vein thrombosis end pulmonary embolism were seen in 4.27% of neurooncological patients treated with bevazicumab alone. In patients treated with bevacizumab and concomitant chemotherapy, VTE were 4.19%, while in patients treated with bevacizuamb, radiotherapy and chemotherapy were 7.46% (Tab. 1). Incidence of serious thromboembolic events between patients

treated with bevacizumab alone, patients treated with bevacizumab plus chemotherapy, and patients treated with bevacizumab plus chemo-radiotherapy was not significantly different (p= 0,091).

The incidences of CNS hemorrages and extracranial bleedings ≥ grade 3 in patients treated with bevacizuamb alone were 0.4%. Regarding patients treated with antiangiogenic and chemotherapy, the intra-extracranial hemorrhages were 0.84% and 0.97% respectively; the percentages of intra-extracranial bleeding in patients treated with combination of bevacizumab, chemotherapy and radiotherapy were 0.74% and 1.11%. While regarding patients treated with bevacizumab and anticoagulant treatment associated, the percentages of intra-extracranial bleeding were 8.2% and 2.3% respectively (Tab. 2). Incidence of serious hemorragic events between patients treated with bevacizumab alone, patients treated with bevacizumab plus chemotherapy, and patients treated with bevacizumab plus chemo-radiotherapy was not significantly different (p= 0,307). Incidence of serious hemorragic events in patients treated with bevacizumab (alone or with other antineoplastic treatments) with anticoagulants was significantly increased compared to patients treated with bevacizumab without anticoagulants (p< 0,001).

Tab. 1 Results for Thrombotic events

BEVACIZUMAB ALONE

Author, year	Grade 1-2	Grade ≥ 3	ALL grade
Chamberlein, 2009	3/22	1/22	4/22
Friedman, 2009	2/84	5/84	7 /84
Niyazi, 2010	-	1/20	1/20
Raizer, 2010	-	1/61	1/61
TOT		**8/187 (4,27%)**	**13/187 (6,95%)**

BEVACIZUMAB + CHEMOTHERAPIES

Author, year	Grade 1-2	Grade ≥ 3	All grade
Vredenburgh, 2007			4/35
Norden, 2008	1/55	5/55	6/55
Kang, 2008			4/27
Bokstein, 2008			0/20
Friedman, 2009	4/79	9/79	13/79
Poulsen, 2009		1/52	1/52
Socinski, 2009		7/106	7/106
Francesconi, 2010			1/6
Scott, 2010		2/24	2/24
Hasselbach, 2010	0/43	4/43	4/43
Sathornsmetee, 2010		3/56	3/56
Thompson, 2010			0/9
Verhoeff, 2010			2/23
Hofer, 2011			4/225

Taillibert, 2011	2/25	2/25
Reardon, 2011	1/25	1/25
TOT	**34/810 (4,19%)**	**54/810 (6,66%)**

BEVACIZUMAB + RADIO-CHEMOTHERAPY

Author, year	Grade 1-2	Gradi ≥ 3	All grade
Lai, 2008		5/10	5/10
Vredenburgh, 2010		2/113	2/113
Vredenburgh, 2011			4/75
Lai, 2011		13/70	19/70
TOT		**20/268 (7,46%)**	**30/268 (11,19%)**

Tab. 2 Results for haemorrhages

BEVACIZUMAB ALONE

Author, year	CNS hemorrhages	Grade	Extra CNS hemorrhages	Grade
Chamberlein, 2009	2/22	2	0/22	-
Friedman, 2009	2/84	1-2	21/84	1-2
Raizer, 2010	1/61	2	2/61	3-4
Niyazi, 2010	0/20	-	0/20	-
Bartolomeo, 2011	2/218	4	0/218	-
	2/218	2		
	3/218	1		
Fraum, 2011	1/88	n.r.	0/88	-
TOT	**13/493 (2,63%)**		**23/493 (4,66%)**	
TOT (Gr ≥3)	**2/493 (0,4%)**		**2/493 (0,4%)**	

BEVACIZUMAB + CHEMOTHERAPIES

Author, year	CNS hemorrhages	Grade	Extra CNS hemorrhages	Grade
Vredenburgh, 2007	1/35	n.r.	0/35	-
Zuniga, 2008	0/51	-	9/51	1-2
Bockenstein, 2008	0/20	-	1/20	2
Norden, 2008	2/55	1	7/55	1-2
Kang, 2008	1/27	n.r.	1/27	n.r.
Poulsen, 2009	1/52	3	11/52	1-2
Taillibert, 2009	6/25	1-2	3/25	1-2
			1/25	3
Socinski, 2009	0/106	-	5/106	3-5
Friedman, 2009	3/79	All	29/79	All
	1/79	≥ 3	1/79	≥ 3
Francesconi, 2009	0/6	-	0/6	-
Scott, 2010	0/24	-	0/24	-
Sathornsumetee, 2010	1/56	1-2	5/56	1-2
			1/56	3
Thompson, 2010	0/9	-	0/9	-
Verhoeff, 2010	1/23	4	0/23	-
Hasselbach, 2010	1/43	1	8/43	1-4
Hofer, 2011	6/225	n.r.	2/225	n.r.
Reardon, 2011	0/25	-	0/25	-
Fraum, 2011	2/73	n.r.	0/73	-
Nghiemphu, 2008	7/244	≥ 3	0/244	-
TOT	**32/1178 (2.71%)**		**83/1178 (7.04%)**	
TOT (Gr ≥3)	**10/1178 (0.84%)**		**11/1126 (0.97%)**	

BEVACIZUMAB + RADIO-CHEMOTHERAPY

Author, year	CNS hemorrhages	Grade	Extra CNS hemorrhages	Grade
Lai, 2008	0/10	-	2/10	1-2
Vredenburgh, 2010	1/113	2	0/113	-
Lai, 2011	2/70	3-4	3/70	3
Vredenburgh, 2011	1/75	2	0/75	-
TOT	**4/268 (1.49%)**		**5/268 (1.86%)**	
TOT (Gr ≥3)	**2/268 (0.74%)**		**3/268 (1.11%)**	

BEVACIZUMAB + ANTICOAGULATION

Nghiemphu, 2008	5/21	all	0/21	-
Bartolomeo, 2011	5/64	1	2/64	3
	2/64	4-5		
TOT	**12/85 (14.1%)**		**2/85 (2.3%)**	
TOT (Gr ≥3)	**7/85 (8.2%)**		**2/85 (2.3%)**	

Discussion

Venous thromboembolism represent one of the most important causes of morbidity (hospitalization, anticoagulation use, bleeding complications, increased risk of recurrent VTE, cancer treatment delays) *(Khorana AA, 2009)* and mortality in cancer patients (*Khorana AA et al, 2006; Chew HK et al, 2006; Chew HK et al, 2007).* Overall, approximately 20% of all VTE cases occur in patients with cancer *(Lee AY, 2005)* and the true extent of this complication may be underestimated *(Lyman GH et al, 2007; Gao S et al, 2004).*

The incidence of DVT and/or PE in patients with a brain tumor was found to be 120:100.000 – the second highest rate for any malignancy *(Levitan N et al, 1999), from Medicare Provider Analysis and Review Record.* Both retrospective and prospective studies have suggested a particularly high incidence of VTE in patients with malignant gliomas *(Constantini S et al, 1991; Sawaya R et al, 1992; Brandes AA et al, 1997),* from 2 to 60%.

The mechanism of VTE development is multifactorial and neuro-oncological patients have many risk factors included histologic diagnosis of glioblastoma multiforme (intraluminal thrombosis in the tumor pathological specimen), larger tumour size (high levels of pro-coagulant factors, use of high-dose steroids and more probability of motor deficit), presence of leg paresis (one of the most consistently identified factor due to the absence of the muscles pump effect with venous stagnation), older age (pro-coagulant factors increase with

age, but anticoagulant proteins remain stable), more lengthy surgery (operative time more than 4 hours), entity of surgery (subtotal resection versus total resection), chemotherapy (it reduces fibrinolytic activity), radiotherapy and steroids (*Marras LC et al, 2000; Semrad TJ et al, 2007).*

Also the novel antiangiogenic agents, as inhibitors of the vascular endothelial growth factor (VEGF), seem to increase the risk of thromboembolic events and haemorrhage.

Because of the significant clinical improvement (Verhoeff) of antiangiogenic therapy in patients with recurrent high grade gliomas, the use of bevacizuamb has increased in clinical practice despite its possible risks, but this possible adverse events should be considered, monitored and better defined.

The mechanism of anti-VEGF of antiangiogenic therapy may explain the development of VTE: it may expose subendothelial procoagulant phospholipids causing thrombosis by inhibitio of VEGF-induced endothelial regeneration. Inhibition of VEGF may also predispose to thromboembolic events increasing hematocrit and thus blood viscosity through the surplus of erythropoietin. Moreover Bevacizumab, with its cytotoxic effect, can increase the release of procoagulant factor by tumour itself and the expression of cytokines which contribute to the development of thrombi. (Nalluri 2011, Kilikcap 2003)(Nalluri 2011, Zachary 2011) (Norden 2001) (Hesser 2044, Nalluri 2011). On the other hand, the mechanism of bleeding is not well known. VEGF is involved in endothelial cell survival and integrity of vascular system, and its inhibition could decrease the repair of damaged endothelial cells (Elice 2012) thus inhibiting the coagulation cascade regulated by tissue factor. Cases of thrombocytopenia in patients treated with bevacizumab and chemotherapy that could predispose to haemorrage are described (Hapani 2010).

Our results seem to show that risk of tromboembolic events does not differ between patients treated with bevacizumab alone and patients treated with bevacizumab plus chemotherapy (4.27% vs 4.19%), while it seems to increase when bevacizumab is associated with chemo-radiotherapy (7.46%). This difference, even if not statistically significant, could be explaned by the fact that patients undergoing concomitant treatment are at higher risk to develop thrombotic events because of the recent neurosurgery and the frequent concomitant steroid therapy in the perioperative setting and during radiotherapy.

If we consider all grade of toxicity (1-5 grade), the percentage increases up to 6.95% for bevacizumab alone and 11.19% when bevacizuamb is associated with chemo-radiotherapy. However the risk linked to antiangiogenetic therapy, although administered alone, remains slightly high for patients with glioma.

It is important to underline that even if our data highlight a thromboembolic risk link to the use of bevacizumab in addition to chemo-radiotherapy, an important phase III study conducted by Roche (AVAglio)[30], designed to evaluate the efficacy and safety of bevacizumab in combination with radio and chemotherapy, has recently completed the enrollment without showing an unaccettable safety profile. We will have the results of this study and the specific data about thromboembolic and hemorrage risk with bevacizumab in concomitant treatment next year.

Regarding ≥3 grade intracranial hemorrhages, there are not significant differences between antiangiogenic therapy administered alone or in combination with radio-chemotherapy (0.6% vs 0.74%), while regarding extracranial bleeding (GI bleeding, epistaxis) data confirmed an increased risk in patients treated with bevacizumab and radio-chemotherapy (0.4% vs 1.11%) . Whereas, considering all grades of toxicity, intra-extracranial bleeding were more frequently seen in patients receiving bevacizumab associated with other chemotherapy (2.71% and 7.04% respectively).

Concomitant anticoagulant treatment seems to increase hemorragic risk of any grade, including severe bleeding. In fact our study shows 8.2% of CNS hemorrhage ≥ 3 in bevacizumab plus anticoagulant; the percentage increases up to 14.1% if we consider all grade of toxicity. On the other hand, regarding extracranial hemorrhage, the percentage is around 2.3% both for all toxicity and for only ≥ 3 grade.

Although bevacizumab is considered one of the best therapy in terms of tolerability, and in 50% of treated patients is also possible to reduce or discontinue corticosteroids therapy with evident clinical benefit, and improvement of quality of life, this anti-VEGF agent has a well-recognized complications that include hypertension, proteinuria, delay in wound healing, and leukoencephalopathy. Our data confirmed also a not negligible risk under thromboembolic/hemorrhagic profile especially in neurooncological patients undergoing chemo-radiotherapy treatment. The hemorrhagic risk is likely to increase in those patients on anticoagulants treatment.

Conclusion

Our analysis confirmed that bevacizumab alone is associated with a slightly high risk for developing a thromboembolic event. Bevacizumab combined with chemo and radiotherapy increases the risk to develop venous thromboembolism. Regarding the use of anticoagulants combined with bevacizumab, our analysis found a significant increase of serious bleedings, both intracranial and extracranial. Our anti-VEGF plus anticoagulants data are based on only two studies (Bartolomeo, Nghiemphu), this could be do to few available information reported for fears of major CNS hemorrhages.

To date, there are also few data and any guidelines on the prevention and management of these complications. Further studies on antiangiogenic toxicities are needed to understand the true risk/benefit ratio of therapy in high grade glioma patients and also the relationship between dose received, duration of treatment and adverse event.

References

1. Bokstein F, Shpigel S, Blumenthal DT (2008) Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. Cancer 112:2267-2273
2. Carden CP, Larkin JM, Rosenthal MA (2008) What is the risk of intracranial bleeding during anti-VEGF therapy?. Neuro Oncol 10:624-630
3. Chamberlain MC (2010) Bevacizumab and irinotecan for recurrent oligodendroglial tumors. Neurology 74:181
4. Chamberlain MC (2009) Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 72:772-3; author reply 773-4
5. Chamberlain MC, Johnston SK (2011) Recurrent spinal cord glioblastoma: salvage therapy with bevacizumab. J Neurooncol 102:427-432
6. Clark AJ, Butowski NA, Chang SM, Prados MD, Clarke J, Polley MY, Sughrue ME, McDermott MW, Parsa AT, Berger MS, Aghi MK (2011) Impact of bevacizumab chemotherapy on craniotomy wound healing. J Neurosurg 114:1609-1616
7. Francesconi AB, Dupre S, Matos M, Martin D, Hughes BG, Wyld DK, Lickliter JD (2010) Carboplatin and etoposide combined with bevacizumab for the treatment of recurrent glioblastoma multiforme. J Clin Neurosci 17:970-974
8. Fraum TJ, Kreisl TN, Sul J, Fine HA, Iwamoto FM (2011) Ischemic stroke and intracranial hemorrhage in glioma patients on antiangiogenic therapy. J Neurooncol
9. Hasselbalch B, Lassen U, Hansen S, Holmberg M, Sorensen M, Kosteljanetz M, Broholm H, Stockhausen MT, Poulsen HS (2010) Cetuximab, bevacizumab, and irinotecan for patients with primary glioblastoma and progression after radiation therapy and temozolomide: a phase II trial. Neuro Oncol 12:508-516

10. Hofer S, Elandt K, Greil R, Hottinger AF, Huber U, Lemke D, Marosi C, Ochsenbein A, Pichler J, Roelcke U, Weder P, Zander T, Wick W, Weller M (2011) Clinical outcome with bevacizumab in patients with recurrent high-grade glioma treated outside clinical trials. Acta Oncol 50:630-635
11. Iwamoto FM, Lamborn KR, Robins HI, Mehta MP, Chang SM, Butowski NA, Deangelis LM, Abrey LE, Zhang WT, Prados MD, Fine HA (2010) Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02). Neuro Oncol 12:855-861
12. Kang TY, Jin T, Elinzano H, Peereboom D (2008) Irinotecan and bevacizumab in progressive primary brain tumors, an evaluation of efficacy and safety. J Neurooncol 89:113-118
13. Lai A, Tran A, Nghiemphu PL, Pope WB, Solis OE, Selch M, Filka E, Yong WH, Mischel PS, Liau LM, Phuphanich S, Black K, Peak S, Green RM, Spier CE, Kolevska T, Polikoff J, Fehrenbacher L, Elashoff R, Cloughesy T (2011) Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 29:142-148
14. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, Prabhu S, Loghin M, Gilbert MR, Jackson EF (2011) Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys 79:1487-1495
15. Niyazi M, Ganswindt U, Schwarz SB, Kreth FW, Tonn JC, Geisler J, la Fougere C, Ertl L, Linn J, Siefert A, Belka C (2010) Irradiation and Bevacizumab in High-Grade Glioma Retreatment Settings. Int J Radiat Oncol Biol Phys
16. Norden AD, Bartolomeo J, Tanaka S, Drappatz J, Ciampa AS, Doherty LM, Lafrankie DC, Ruland S, Quant EC, Beroukhim R, Wen PY (2011) Safety of concurrent bevacizumab therapy and anticoagulation in glioma patients. J Neurooncol
17. Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, Ciampa AS, Ebbeling LG, Levy B, Drappatz J, Kesari S, Wen PY (2008) Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 70:779-787
18. Reardon DA, Desjardins A, Peters KB, Vredenburgh JJ, Gururangan S, Sampson JH, McLendon RE, Herndon JE,2nd, Coan A, Threatt S, Friedman AH, Friedman HS (2011) Phase 2 study of carboplatin, irinotecan, and bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy. Cancer
19. Sathornsumetee S, Desjardins A, Vredenburgh JJ, McLendon RE, Marcello J, Herndon JE, Mathe A, Hamilton M, Rich JN, Norfleet JA, Gururangan S, Friedman HS, Reardon DA (2010) Phase II trial of bevacizumab and erlotinib in patients with recurrent malignant glioma. Neuro Oncol 12:1300-1310
20. Socinski MA, Langer CJ, Huang JE, Kolb MM, Compton P, Wang L, Akerley W (2009) Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. J Clin Oncol 27:5255-5261
21. Stupp R, Hegi ME, Neyns B, Goldbrunner R, Schlegel U, Clement PM, Grabenbauer GG, Ochsenbein AF, Simon M, Dietrich PY, Pietsch T, Hicking C, Tonn JC, Diserens AC, Pica A, Hermisson M, Krueger S, Picard M, Weller M (2010) Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. J Clin Oncol 28:2712-2718

22. Taillibert S, Vincent LA, Granger B, Marie Y, Carpentier C, Guillevin R, Bellanger A, Mokhtari K, Rousseau A, Psimaras D, Dehais C, Sierra del Rio M, Meng Y, Laigle-Donadey F, Hoang-Xuan K, Sanson M, Delattre JY (2009) Bevacizumab and irinotecan for recurrent oligodendroglial tumors. Neurology 72:1601-1606
23. Verhoeff JJ, Lavini C, van Linde ME, Stalpers LJ, Majoie CB, Reijneveld JC, van Furth WR, Richel DJ (2010) Bevacizumab and dose-intense temozolomide in recurrent high-grade glioma. Ann Oncol 21:1723-1727
24. Vredenburgh JJ, Desjardins A, Kirkpatrick JP, Reardon DA, Peters KB, Herndon JE,2nd, Marcello J, Bailey L, Threatt S, Sampson J, Friedman A, Friedman HS (2010) Addition of Bevacizumab to Standard Radiation Therapy and Daily Temozolomide Is Associated with Minimal Toxicity in Newly Diagnosed Glioblastoma Multiforme. Int J Radiat Oncol Biol Phys
25. Vredenburgh JJ, Desjardins A, Reardon DA, Peters KB, Herndon JE,2nd, Marcello J, Kirkpatrick JP, Sampson JH, Bailey L, Threatt S, Friedman AH, Bigner DD, Friedman HS (2011) The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res 17:4119-4124
26. Zuniga RM, Torcuator R, Jain R, Anderson J, Doyle T, Ellika S, Schultz L, Mikkelsen T (2009) Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. J Neurooncol 91:329-336
27. Armstrong TS, Wen PY, Gilbert MR, Schiff D Management of treatment-associated toxicites of anti-angiogenic therapy in patients with brain tumors. Neuro Oncol. 2012 Feb 15.
28. Elice F, Rodeghiero F. Side effects of anti-angiogenic drugs. Thromb Res. 2012 Apr;129 Suppl 1:S50-3.
29. Hapani S, Sher A, Chu D, Wu S. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology. 2010;79(1-2):27-38. Epub 2010 Nov 3. Review.
30. Chinot OL, de La Motte Rouge T, Moore N, Zeaiter A, Das A, Phillips H, Modrusan Z, Cloughesy T AVAglio: Phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. Adv Ther. 2011 Apr;28(4):334-40. Epub 2011 Mar 14.