D-Dimer Elevation and Paresis Predict Thromboembolic Events During Bevacizumab Therapy for Recurrent Malignant Glioma

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Abstract. *Background: The major side-effects of bevacizumab in glioma treatment are venous thromboembolic events (VTE). We retrospectively evaluated factors potentially predictive of thromboembolic events. Patients and Methods: Bevacizumab, alone or in combination with chemotherapy was used as salvage therapy for recurrence in malignant glioma every two weeks. None but one patient received anti-coagulants. Before each bevacizumab cycle differential blood cell count, kidney and liver parameters, D-dimers, neurological status, body-mass index, vital signs and signs of venous thrombosis were assessed. Results: Thirty-eight patients received 428 cycles of bevacizumab. In five patients (13%), six VTE were observed. These complications were preceded four weeks before the onset of symptoms by D-dimer elevation above 0.865 mg/l [p<0.0001; sensitivity=89% (95% confidence interval=83-93%); specificity=89% (95% CI=52-100%)]. An existing hemiparesis constituted a 27-fold risk elevation for thrombotic complication (p<0.0001, χ^2-test). Conclusion: D-Dimer elevation or hemiparesis predict VTE under bevacizumab and chemotherapy, four weeks before the event becomes clinically apparent. Future investigations should determine if prophylactic anti-coagulants for patients at risk may reduce the risk of VTE.*

Despite advances in operative techniques and radiochemotherapy, malignant gliomas (WHO grade III and WHO grade IV) still carry a dismal prognosis (1, 2). Seeking anti-angiogenic treatments, bevacizumab, a monoclonal humanized antibody which binds and inactivates free vascular endothelial growth factor (VEGF), was introduced. Due to a diversity of phase-II studies for recurrent malignant glioma, bevacizumab, as single-agent or in combination with cytotoxic drugs, was widely used as salvage therapy (3-6). However, despite approval by the Food and Drug Administration (FDA) in the US, the European Medicines Agency (EMEA) declined approval due to a lack of phase III trials (7). Therefore, in Europe the use of bevacizumab is restricted to selected patients, often after fully-utilized treatment consisting of temozolomide rechallenge (8-10) and nitrosourea-based protocols (11, 12) and when, on an individual basis, the patient's health insurance beard the costs for off-label use.

The first results of a randomized placebo controlled trial (13), introducing bevacizumab in addition to first-line concomitant and adjuvant temozolomide radiochemotherapy, revealed prolonged progression-free survival (14). In respect to these data, bevacizumab might shortly advance as standard first-line treatment for glioblastoma. Thus, the use of bevacizumab for glioblastoma is expected to increase, and consecutively bevacizumab-associated morbidity will become an issue.

In the setting of bevacizumab therapy, venous thrombotic events (VTE) in up to 26% of patients constitute major side-effects, with the risk of life-threatening events (15, 16). This high incidence urges the establishment of parameters anticipating these thrombotic complications. For patients with solid chemo-naïve non-brain tumors, a score anticipating VTE has been introduced (17). However, there are no scores focusing on patients with glioma often suffering from neurological deficit, receiving steroids, bevacizumab and additional cytotoxic agents, which in combination results in a very high risk for VTE. D-Dimers are routinely used to detect VTE in patients when clinical signs raise suspicion for such complications in oncology patients (18, 19). In our institution, D-dimers are quantified routinely before each bevacizumab administration. In this report, we retrospectively assessed the predictive potential of D-dimers and clinical findings for VTE in patients with glioma under bevacizumab therapy.

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Key Words: Recurrent malignant glioma, bevacizumab, deep venous thrombosis, D-dimer.

Patients and Methods

Thirty-eight consecutive patients receiving bevacizumab for recurrent malignant glioma were included in the present retrospective analysis. There were no patients excluded. The local Ethics Committee gave approval for this study (EA2/007/10).

The previous treatment consisted of radiotherapy in all patients, temozolomide in 37 (97%), temozolomide re-challenge in 16 (42%) of which 12 (32%) were applied metronomically as an anti-angiogenic regimen, sunitinib in five (13%), nitrosourea in two (8%) and enzastaurin in one (3%) patient. Twenty-two patients (55%) had more than one prior chemotherapy regime. Four patients (10%) received re-irradiation and 26 patients (68%) underwent re-operation (Table I).

At initiation of bevacizumab treatment, the median patient age was 54.5 (range=29-71) years. For analysis, patients had to have undergone at least three cycles of bevacizumab treatment.

All patients received bevacizumab at 10 mg/kg body weight every 14 days. No dose reduction was necessary. Concomitant chemotherapy consisted of irinotecan at 125 mg/m^2 body surface in 29 patients (76%) and low-dose continuous temozolomide in nine patients (24%) at 10 mg/m^2 body surface *b.i.d.* For irinotecan, two dose reductions of 25% were allowed before discontinuation of the agent in cases of uncontrollable fatigue, nausea, diarrhea or hematological toxicity. Differential blood cell count, kidney and liver parameters, D-dimers, neurological status, body-mass index, vital signs and signs of venous thrombosis according to the Revised Geneva criteria (20) were routinely assessed before every bevacizumab administration as a standard-of-care. On suspicion of deep venous thrombosis (unilateral extremity swelling, extremity pain, temperature difference of the extremities) or pulmonary embolism (dyspnea, tachycardia), a Doppler ultrasound of the extremities or pulmonary Computed Tomography (CT) scan was carried out, respectively. VTE was defined as detectable clot by ultrasound in superficial or deep veins of the upper and lower extremities that caused clinical symptoms.

Magnetic Resonance Imaging (MRI) scans were performed every eight weeks. Bevacizumab-based therapy was continued until radiological tumor progression in contrast T1 or Fluid Attenuation Inversion Recovery (FLAIR) imaging, clinical signs of tumor progression, severe drug-related complications or decline of the patient's general condition.

For this analysis, a VTE was the primary end-point, defined as clinical evidence for venous thrombosis or pulmonary embolism and confirmation by ultrasound or CT scan. Potential predictive factors were analyzed four weeks prior to these events. Student's *t*-test, receiver operating characteristics (ROC) and χ^2 test were used for statistical analysis. Due to the small absolute number of patients with events, multivariate analysis was not carried out. The tests were performed with the GraphPad Prism version 5.00 for MacOS (GraphPad Software, San Diego, CA, USA; www.graphpad.com).

Results

Thirty-eight patients received 428 cycles of bevacizumab. Three patients (8%) withdrew from therapy due to unbearable side-effects (fatigue) before tumor progression. We observed six VTEs in five patients (13%), consisting of one sinus vein thrombosis, one pulmonary embolism, two deep-vein thromboses and one combination of the latter two (Table I). The revised Geneva criteria (20) identified two patients as being at high-risk (revised Geneva score (rGS) > 11) for the presence of thrombosis in which diagnosis was confirmed by ultrasound or pulmonary CT scan. The other three symptomatic patients were rated as being at intermediate-risk (rGS 4-10), as were all the other 33 patients, who did not develop VTE. None of the patients was assigned to be at low risk (rGS 0-3). The predictive risk score identified three patients as being at high-risk, of whom only one developed thrombosis. The other four symptomatic patients were rated as being at intermediate-risk.

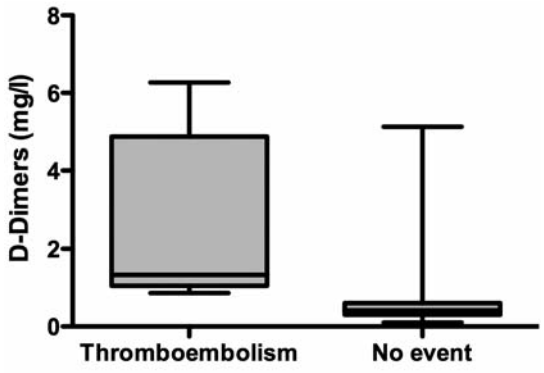

Figure 1. *Box-plot of D-dimer levels in patients with and without thromboembolic events under bevacizumab plus chemotherapy ($p<0.0001$). bar: median, box: upper and lower quartile, whiskers: minimum and maximum.*

D-Dimers four weeks prior to VTE were higher compared to an event-free course (no VTE) in this interval (2.9 and 0.5 mg/l, respectively; $p<0.0001$, *t*-test, Figure 1). All patients suffering from VTE had D-dimers ≥0.86 mg/l four weeks before the onset of symptoms. ROC analysis revealed a cut-off value of 0.865 mg/l (area under the ROC curve 0.9612; $p<0.0001$, Figure 2) predicting a VTE with a sensitivity of 88.9% (95% confidence interval (CI)=83.7-92.9%) and specificity of 88.9% (95% CI=51.8-99.7%). D-Dimers below the cut-off value ruled-out a VTE within four weeks with a probability of 99.7% (95% CI=98.5-99.9%).

Four out of five patients suffered from hemiparesis before VTE (three patients with degree 4 and one patient with degree 2, according to the Medical Research Council (21)). Absence of hemiparesis defined as degree 4+ or better also ruled-out a VTE with a probability of 99.7% (95% CI=98.5-99.9%). Thus, an existing hemiparesis constituted a 27-fold increased risk for VTE within four weeks ($p<0.0001$, χ^2 test). Body-mass index did not constitute an independent risk factor for VTE ($p=0.638$). Although the male-to-female ratio of VTE incidence was 2:3, the female gender did not influence the risk for VTE.

Table I. *Patients' characteristics, scores and individual risk factors. In parentheses initial diagnosis, if different from later histology.*

Patient#	Age	Gender	ECOG	Histology	Treatment course	Events	Khorana risk score (17)	Revised Geneva risk score (20)	BMI	Hemi-paresis	Incomplete resection	CTX	Event within 61 days of operation	>3 Comor-bidities
1	33	M	0	AOA	Res-TMZ-Res-RTX-TMZ-Res-AVA/TMZ		2	5	28	N	N	Y	Y	N
2	56	M	1	GBM	Res-TMZ-RTX-Res-AVA/TMZ		3	5	23	Y	Y	Y	Y	N
3	59	F	0	GBM	Res-TMZ-Res-LDTMZ-AVA/TMZ		2	8	29	Y	Y	Y	N	N
4	42	M	0	GBM	Res-TMZ-AVA/TMZ		2	5	31	N	Y	Y	N	N
5	46	F	2	AOA	BX-RTX-Res-Res-TMZ-BX-AVA/IR		2	5	22	Y	Y	Y	Y	N
6	70	F	2	GBM	Res-TMZ-Res-AVA/TMZ		2	6	20	N	Y	Y	Y	N
7	58	F	1	GBM	Res-RTX+Enz-LDTMZ-AV/TMZ		2	5	26	N	Y	Y	N	N
8	65	M	1	GBM	Res-TMT-AVA/TMZ		2	5	28	Y	N	Y	N	N
9	58	M	2	GBM	Res-TMZ-Res-Sun-AVA/IR	LAE/DVT	2	11	30	Y	Y	Y	N	Y
10	55	M	0	mGBM	Res-TMZ-Res-AVA/IR		2	5	25	N	N	Y	Y	N
11	55	M	0	mGBM	BX-TMZ-LDTMZ-AVA/IR	LAE	2	11	25	Y	Y	Y	N	Y
12	39	M	2	AA	Res-RTX-TMZ-Res-LDTMZ-AVA/IR		2	5	30	N	Y	Y	N	N
13	50	F	2	GBM	Res-TMZ-Res-LDTMZ-Res-AVA/IR		2	5	31	Y	N	Y	Y	Y
14	50	F	2	GBM (AA)	Res-RTX-TMZ-BX-TMZ-AVA/IR	DVT	3	9	27	Y	Y	Y	Y	N
15	71	M	0	GBM	Res-TMZ-Res-AVA/IR		2	6	25	N	N	Y	Y	Y
16	54	M	0	GBM	Res-TMZ-Res-LDTMZ-Res-AVA/IR	Appendicitis	2	5	23	N	Y	Y	Y	N
17	56	M	1	GBM	Res-TMZ-Res-Sun-AVA/IR		2	5	16	N	Y	Y	N	Y
18	41	M	2	GBM	Res-TMZ-AVA/IR	Wound infection	3	5	31	Y	Y	Y	N	Y
19	38	F	0	GBM (O)	Res-Res-RTX-TMZ-BX-AVA/IR	DVT	2	5	27	Y	Y	Y	Y	N
20	53	F	2	GBM (A)	Res-Res-RTX-RTX-BX-TMZ-AVA/IR		2	9	24	Y	Y	Y	Y	N
21	66	F	0	GBM	Res-TMZ-AVA/IR		2	5	25	N	Y	Y	N	N
22	58	F	1	GBM	Res-TMZ-Res-Sun-AVA/IR		2	6	27	N	Y	Y	N	Y
23	52	F	2	GBM	Res-TMZ-Res-TMZ-AVA/IR	SVT	2	5	25	N	Y	Y	N	Y
24	57	M	0	mGBM	Res-TMZ-AVA/IR		2	5	28	N	Y	Y	N	N
25	49	M	1	mGBM	Res-TMZ-Sun-AVA/IR		2	5	27	N	Y	Y	N	N
26	51	M	1	GBM	Res-TMZ-Sun-AVA/IR		2	5	31	Y	N	Y	N	Y
27	54	M	0	AA	Res-RTX-Res-AVA/IR		2	5	23	N	Y	N	N	N
28	56	M	0	GBM	Res-TMZ-Res-AVA/IR		2	5	26	Y	N	Y	Y	N
29	56	F	1	GBM (A)	Res-RTX-RTX-TMZ-BX-LDTMZ-Res-AV/IR		2	5	20	N	Y	Y	Y	N
30	66	M	1	GBM	Res-TMZ-Res-TMZ-AVA/IR	Bowel perforation	2	6	22	N	Y	Y	N	N
31	29	F	1	mGBM	Res-TMZ-Res-LDTMZ-AVA/TMZ		2	5	23	N	Y	Y	N	N
32	30	M	0	GBM	Res-TMZ-Res-LDTMZ-Res-AVA/IR		2	5	25	N	N	Y	Y	N
33	46	F	0	GBM	Res-TMZ-Res-LDTMZ-RTX-AVA/IR		2	5	28	N	Y	Y	N	N
34	33	M	1	GBM (A)	Res-Res-RTX-TMZ-Res-LDTMZ-Res-PCV-AVA/IR		2	5	28	N	Y	Y	N	N
35	62	M	1	AA	Res-RTX-Res-PCV-Res-TMZ-Res-AVA/IR		2	5	21	Y	Y	Y	N	N
36	62	M	2	AA	BX-RTX-BX-TMZ-Res-AVA/TMZ	Hip joint empyema	2	5	30	N	Y	Y	Y	N
37	56	M	0	GBM	Res-TMZ-AVA/IR		2	5	31	N	Y	Y	N	N
38	47	F	1	AO	Res-Res-RTX-TMZ-LDTMZ-AVA/IR		2	5	23	N	Y	Y	N	N

A, Astrocytoma WHO°II; AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AVA/IR, bevacizumab + irinotecan; AVA/TMZ, bevacizumab + temozolomide; BMI, body-mass index; BX, biopsy only; CTX, any chemotherapy prior to bevacizumab with chemotherapy; DVT, deep-vein thrombosis; ECOG, Eastern Cooperative Oncology Group performance status; Enz, enzastaurin; F, female; GBM, glioblastoma multiforme; LAE, lung artery embolus; LDTMZ, low-dose temozolomide 20 mg b.i.d. plus celecoxib; M, male; mGBM, multifocal GBM; O, oligidendroglioma WHO°II; PCV, procarbazine + lomustine + vincristine; Res, resection; RTX, radiotherapy; Sun, sunitinib; SVT, sinus vein thrombosis; TMZ, temozolomide 5/28 days.

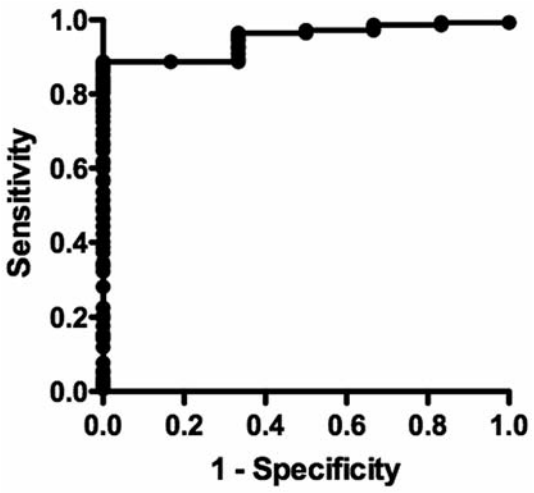

Figure 2. *Receiver operating characteristic (ROC) curve of D-dimer levels and calculated cut-off point of 0.865 mg/l (area under the ROC curve=0.9612).*

The one patient (Table I, #14) with the anticoagulant nadroparin at 2,850 IU/0.3 ml *o.d.* was at intermediate-risk and still developed a deep venous thrombosis preceded by a hemiparesis and D-dimers of 4.26 mg/l.

Discussion

In this series, VTE occurred in 13% of patients with glioma treated with bevacizumab. These results are in line with incidence rates of 5 to 23% in previous reports of bevacizumab for recurrent glioma (3, 4, 22, 23). Presuming a VTE rate of 7.5% in patients not treated with bevacizumab, including these with poor general condition and perioperative events (24), these data depict the high morbidity of additional bevacizumab. In the future, even higher VTE rates can be anticipated, as 90% of VTE in patients not treated with bevacizumab occur within the first six months after initial diagnosis (25). In fact, a pilot study with 10 patients implementing first-line bevacizumab with standard radiochemotherapy reported a VTE rate of 30% (26). This stresses out the need to identify predictive factors for VTE. However, to reduce the influence of postoperatively associated VTE in our analysis, patients were only included six weeks after eventual surgery, corresponding to three cycles of bevacizumab.

The proposed mechanism causing these coagulation disorders is a disturbance of endothelial homeostasis by VEGF antibodies, since VEGF has a maintenance role in normal endothelial function (27). Endothelial apoptosis may expose the vascular, highly pro-thrombotic, basement membrane. Moreover, VEGF signaling seems to essentially produce platelet inhibitors, such as prostaglandin-1 and -2 and nitric oxide (28). VEGF and bevacizumab also induce platelet aggregation by forming antibody complexes, leading to pro-thrombotic effects (29, 30).

Counteracting these pro-thrombotic effects with anti-platelet or anticoagulant agents may increase the risk of hemorrhagic events. However, patients on aspirin to prevent arterial thromboembolic events did not significantly experience more bleeding events (31). Even warfarin medication did not seem to increase bleeding complications in bevacizumab-treated patients with colorectal cancer or glioma (15, 31). Low-molecular weight heparin is another effective anti-coagulant to prevent VTE in patients with glioma (32). A prospective study examining the effects of thrombosis prophylaxis in patients with glioma showed a trend for risk reduction in the treatment group, but at the cost of increased risk of cerebral hemorrhage (33). These findings urge that parameters be sought anticipating thromboembolism, in order to implement prophylactic therapy targeted to the patients at risk.

D-Dimer elevation beyond the calculated cut-off value preceded thrombosis by four weeks, acting as valuable predictive factor. However, these data do not prove that thrombosis was necessarily a direct effect of bevacizumab therapy. In fact, in other types of cancer D-dimers indicate tumor load (34), but did not indicate tumor recurrence in our study. Due to the multiple factors contributing to thrombosis, D-dimers might function as a surrogate of clinical value. A causal role of D-dimers would raise the need for a matched or randomized control group without bevacizumab treatment. As the patients reported here were qualified for bevacizumab treatment especially by their good general condition, a control group would have a strong bias concerning VTE, interfering with eventual analysis.

There are further known risk factors for VTE in patients with gliomas. Old age, histology of glioblastomas, residual tumor mass and comorbidities have been reported as being associated with VTE (24, 25). However, in our study most patients have had a glioblastoma, with residual tumor and comorbidities, without experiencing VTE, so we would have not been able to identify the 5 patients with VTE in our study (Table 1). The major drawback of age, histology, residual tumor and comorbidity as predictor for TVE, is the inability to change according to the patient's current constitution. According to the AVAglio study results, we expect average bevacizumab applications of 10.6 months (14), thus a dynamic updated risk evaluation is desirable. Both D-dimers and the existence of paresis are easy to re-evaluate and reveal a prediction of VTE for the following four weeks, with a specifity and sensitivity of 89%, each. The specificity should be treated with caution, however as, due to the small absolute number of VTE in our series, the 95% CI is wide, from 51.8-99.7%.

In prospective future studies, the effect of anti-coagulants in patients with either paresis or elevated D-dimers should be evaluated.

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