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Research Article

Neurosurgical Complications in Patients under Bevacizumab Therapy

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Abstract

The anti-VEGF humanized monoclonal antibody bevacizumab is increasingly used, either alone or in combination with chemotherapeutic agents, in cancer therapy. Side-effects of bevacizumab particularly relevant to the surgeon include hemorrhage and delayed wound-healing. Current guidelines are largely empiric and recommend that bevacizumab be discontinued for 4 to 8 weeks before elective surgery. Little is known about the risks of neurosurgical procedures in patients receiving bevacizumab.

We retrospectively reviewed surgical complications in patients who underwent a neurosurgical intervention following a therapy with bevacizumab 3 month or less prior to surgery or received bevacizumab within 3 months after a surgical intervention at our institution. Ninety-six patients who had received bevacizumab for different malignant diseases were operated at our department between August 2008 and August 2013. Forty-one neurosurgical interventions of any type were performed in 36 patients from this cohort. Nine interventions were performed 28 days or less after the last bevacizumab application (early and emergency surgery group). Twelve patients underwent surgery in an interval ranging from 28 days to 3 months after the last bevacizumab application (elective surgery group). One severe bleeding complication occurred in a patient from the early and emergency surgery group who underwent exchange of a ventriculo-peritoneal shunt 7 days after the last application of bevacizumab. One bacterial meningitis and one delayed wound-healing occurred in the elective surgery group. Two wound-healing complications were noted in 21 patients who were treated with bevacizumab within 3 months after surgery.

Our data support the notion that preoperative bevacizumab treatment – especially if the interval between bevacizumab therapy and surgery is short – carries a risk for surgical complications. With a delay of 4 weeks, elective neurosurgery seems to be safe following bevacizumab treatment.

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INTRODUCTION

Vascular endothelial growth factor (VEGF) plays an important role in tumor growth by enhancing the formation of abnormal tumor vasculature [1,2]. Bevacizumab, a humanized monoclonal antibody that inhibits VEGF activity is increasingly used alone or in combination with chemotherapy in the treatment of various cancers including colorectal cancer, non-small cell lung cancer, breast cancer, ovarian cancer, renal cell carcinoma and glioblastoma multiforme (GBM). While survival benefit has been clearly proven in other solid tumors [3,4] the value of bevacizumab in GBM therapy is still unclear [5]. Bevacizumab was first evaluated in the treatment of recurrent GBM and on the basis of promising results of phase II trials accelerated approval by the US Food and Drug Administration for bevacizumab therapy in recurrent GBM was granted [6]. Recently, two international multicenter randomized phase III trials, RTOG 0825 and AVAglio, have demonstrated a significant improvement in progression free survival for patients with GBM when bevacizumab is added to standard treatment as a first line therapy. However, a survival benefit has not been proven [7,8].

Because of the important physiological roles of VEGF [9], its inhibition by bevacizumab can cause serious adverse events different from traditional cytotoxic chemotherapy [10]. Frequently reported side-effects include hypertension, proteinuria, hemorrhage, gastro-intestinal tract perforation, wound healing complications, arterial and venous

thromboembolism, reversible posterior leukoencephalopathy, neutropenia, infections, nephrotic syndrome, and congestive heart failure [11]. Large meta-analyses have shown an increased treatment-related mortality and bleeding risk in patients receiving bevacizumab [12], [13]. Side-effects of bevacizumab therapy especially relevant to the surgeon comprise an increased bleeding risk and wound-healing complications [14,15]. Several studies from various surgical disciplines have found high rates (up to 63%) of impaired wound healing in patients receiving preoperative bevacizumab [16–19]. Postoperative bevacizumab does not seem to be associated with an increased rate of surgical complications [6,20,21]. The risk for spontaneous intracranial hemorrhage is not increased both in patients treated with bevacizumab for GBM and patients receiving bevacizumab for other solid tumors [22,23].

Few reports exist on the risks of emergency surgery in patients under bevacizumab therapy and no studies dedicated to this issue in neurosurgical patients have been publish to date [24]. Previous work focussing on neurosurgical patients has found a shorter postoperative survival and an increased perioperative morbidity including a very high rate of wound healing complications in GBM patients treated with bevacizumab before repeat craniotomy [25,26]. Because of the very limited knowledge about the risks associated with bevacizumab therapy in neurosurgical patients we report our experience in patients treated with bevacizumab before or after a neurosurgical intervention.

MATERIALS AND METHODS

We performed a retrospective analysis of patients who were treated with bevacizumab and underwent neurosurgical procedures. We included all patients who underwent a neurosurgical intervention at the University of Freiburg between August 2008 and August 2013 and received systemic bevacizumab therapy for various cancers within three months either before or after surgery. Their clinical patient records and radiological studies were reviewed for different clinical data including information about neurological performance and wound healing status, signs of hemorrhage in CT and MRI studies, routine clinical and laboratory coagulation tests (platelet and erythrocyte count, Quick and PTT values, bed side bleeding time tests). The index operation is defined as the neurosurgical procedure performed within 3 months either before or after systemic bevacizumab application.

Patients were subdivided in three groups. Patients receiving bevacizumab prior to the index operation were included in the "early and emergency surgery group" (Table 1) if the last dose of bevacizumab was given 0 to 28 days before surgery or in the "elective surgery group" (Table 2) if the last dose of bevacizumab was given 28 to 90 days before the index operation. Patients receiving bevacizumab between 0 to 90 days after the index operation were included in the "post operative bevacizumab therapy group" (Table 3). Patients with a history of bevacizumab therapy more than 90 days before or after a neurosurgical intervention were excluded from this study.

RESULTS

Patient characteristics

Ninety-six patients who received bevacizumab either before or after surgery underwent a neurosurgical intervention at the University of Freiburg between August 2008 and August 2013. Thirty-six patients met the above mentioned criteria and were included in the present study. The mean age of the patients was 54.2 years (range 18 – 74 years). Twenty patients (56%) were male and 16 (44%) female. The indication for bevacizumab was supratentorial glioblastoma in 32 (89%), low-grade glioma of the brainstem in 1, metastatic colorectal cancer in 2 and metastatic breast cancer in 1 patient. Twenty patients received bevacizumab preoperatively, 9 within 28 days prior to surgery with a mean delay of 14 days (range 0-27 days) (early and emergency surgery group). Twelve patients received bevacizumab between 28 and 90 days prior to surgery with a mean delay of 46 days (range 31 - 83 days) (elective surgery group). One patient (# 9) underwent two stereotactic procedures following bevacizumab therapy and therefore is listed both in the early and emergency surgery group as well as in the elective surgery group with two different index operations. Twenty-one patients received bevacizumab postoperatively within 90 days and a mean delay of 40 days (range 24 – 62 days). Five patients appear in both the pre- and postoperative groups. Bevacizumab was continued after the index operation in 1 patient (# 11) after surgery. Four other patients (# 4, 17, 18 and 19) are listed in both the pre- and postoperative groups with a different index operation. Routine coagulation laboratory tests (Quick, PTT), thrombocyte and erythrocyte counts were within normal ranges in all patients prior to surgery.

Early and emergency surgery

Procedures and Complications in Patients with 0-28 days of Discontinuation of Preoperative Bevacizumab Therapy

Nine patients who had received bevacizumab therapy preoperatively underwent a neurosurgical intervention with a discontinuation of bevacizumab of less than 28 days prior to surgery (Table 1). The surgical procedures were: one craniotomy for cerebral metastasis and two second craniotomies for recurrent glioblastoma, one implantation and one exchange of a ventriculo-peritoneal shunt, one minimally invasive decompression for a herniated lumbar disc, one dorsal multi-level decompression of a metastasis at the thoracic spine, one stereotactic biopsy and one explantation of a ventricular catheter and Rickham reservoir. One surgical complication occurred in this early and emergency surgery group: A 43-year-old patient with a glioblastoma who had received 1 cycle of bevacizumab 5 mg/kg 7 days before suffered from hydrocephalus due to malfunction of a previously implanted ventriculo-peritoneal shunt. Exchange of the entire ventriculo-peritoneal shunt was performed. As a severe complication of this emergency procedure, he developed intracerebral and intraventricular hemorrhage (Figure 1a) and subcutaneous ecchymoses (Figure 1b) in the course of the tunnelled shunt catheter. The case is described in detail in the figure legend.

Elective Surgery: Procedures and Complications in Patients with 28-90 days of Discontinuation of Preoperative Bevacizumab Therapy.

Twelve patients underwent a neurosurgical intervention following bevacizumab therapy with a discontinuation of

Table 1: Early and emergency surgery (discontinuation of bevacizumab 0-28 days prior to surgery).

Patient #	Age at index operation	Diagnosis	Delay between last bevacizumab dose and surgery (d)	Surgical procedure	Complications
1	18,3	Low grade glioma, brainstem	0	Implantation of a ventriculo-peritoneal shunt	None
2	53,6	Cerebral metastasis	14	Resection	None
3	53,1	Extradural spinal metastasis	15	Resection	None
4	40,1	GBM	7	Removement of a ventricular catheter and Rickham reservoir	None
5	74,4	GBM	21	2nd craniotomy, resection	None
6	43,7	GBM	7	Exchange of a ventriculo-peritoneal shunt	Intraventricular hemorrhage and hemorrhage in the trajectory of the ventricular catheter
7	62,8	GBM	27	2nd craniotomy, resection	None
8	58,9	Lumbar disc herniation	21	Minimally invasive dorsal decompression and resection of herniated lumbar disc	None
9§	59,5	Cerebral metastasis	15	Stereotactic biopsy, Implantation of a Iodine-125 Seed	None

Table 2: Elective surgery (discontinuation of bevacizumab 28-90 days prior to surgery).

Patient #	Age at index operation	Diagnosis	Delay between last bevacizumab dose and surgery (d)	Surgical procedure	Complications
10	47,6	GBM	38	Implantation of a ventriculo-peritoneal shunt	None
11*	67,1	GBM	83	2nd craniotomy, resection	Bacterial meningitis
12	65,2	GBM	63	2nd craniotomy, resection	None
13	64,8	GBM	41	2nd craniotomy, resection	None
14	64,6	GBM	33	2nd craniotomy, resection	None
15	71,6	GBM	32	2nd craniotomy, resection	Wound-healing complication, CSF leakage
16	66,0	GBM	34	2nd craniotomy, resection	None
17	46,3	GBM	35	2nd craniotomy, resection	None
18	44,1	GBM	47	2nd craniotomy, resection	None
19	50,8	GBM	31	2nd craniotomy, resection	None
20	69,6	GBM	62	2nd craniotomy, resection	None
9§	59,5	Cerebral metastasis	49	Explantation of Iodine-125 Seed	None

bevacizumab between 28 and 90 days (Table 2). There were 10 second craniotomies for recurrent glioblastoma, one implantation of a ventriculo-peritoneal shunt and one removal of an Iodine-125 seed for brachytherapy. Bacterial meningitis occurred in one patient (#11) who underwent second craniotomy. He was cured by intravenous administration of antibiotics for 10 days. Another patient (#15) developed a small wound dehiscence and leakage of cerebrospinal fluid (CSF) following second craniotomy. The wound dehiscence was closed by a single suture and showed normal secondary healing and the CSF leakage was halted.

Procedures and complications in patients with postoperative bevacizumab therapy

Twenty-one patients received bevacizumab within 90 days after surgery (Table 3). All patients were treated for glioblastoma. There were 15 first and 3 second craniotomies, one explantation of a cranioplastic, one implantation of a ventriculo-peritoneal shunt and one implantation of a ventricular catheter connected to a Rickham reservoir. The latter patient developed a wound-healing complication 4 months later while on bevacizumab therapy. In this patient, the ventricular catheter and Rickham reservoir were removed and surgical debridement of the wound was performed. Thereafter, wound-healing was normal. One patient (#11) who underwent craniotomy and tumor resection 4 months earlier suffered from osteomyelitis of the bone flap while receiving bevacizumab treatment. The bone flap was removed, skull reconstruction with a palacos implant was performed and further healing was regular.

DISCUSSION

In this study, we retrospectively reviewed surgical complications in patients treated with bevacizumab within 3

Table 3: Post operative bevacizumab therapy (bevacizumab therapy 0-90 days following surgery).

Patient #	Age at index operation	Diagnosis	Delay between surgery and first bevacizumab dose (d)	Surgical procedure	Complications
4	39,7	GBM	24	Implantation of a ventricular catheter and Rickham reservoir	Wound-healing complication
11*	67,1	GBM	35	2nd craniotomy, resection	Osteomyelitis
21	54,8	GBM	30	Craniotomy, resection	None
17	45,3	GBM	40	Craniotomy, resection	None
18	62,2	GBM	31	Craniotomy, resection	None
22	70,4	GBM	33	Craniotomy, resection	None
19	49,8	GBM	39	Craniotomy, resection	None
23	73,9	GBM	35	Craniotomy, resection	None
24	19,6	GBM	36	Craniotomy, resection	None
25	61,8	GBM	62	Craniotomy, resection	None
26	61,8	GBM	27	Craniotomy, resection	None
27	48,7	GBM	42	Craniotomy, resection	None
28	40,0	GBM	27	Craniotomy, resection	None
29	49,8	GBM	24	Craniotomy, resection	None
30	57,6	GBM	37	Craniotomy, resection	None
31	52,4	GBM	42	Implantation of a ventriculo-peritoneal shunt	None
32	27,8	GBM	35	Explantation of a cranioplastic	None
33	54,9	GBM	60	Craniotomy, resection of extraaxial tumor	None
34	51,1	GBM	51	Craniotomy, resection	None
35	55,2	GBM	60	2nd craniotomy, resection	None
36	51,5	GBM	62	2nd craniotomy, resection	None

months before or after a neurosurgical intervention. Due to the long half-life of bevacizumab (20 days [27]) discontinuation of 4 to 8 weeks prior to surgery is recommended. Little is known about the risks of neurosurgery under bevacizumab therapy [20]. To our knowledge, this is the first report addressing the risks of emergency neurosurgical interventions in patients receiving bevacizumab. We observed one major complication in the early and emergency surgery group of 9 patients who underwent a neurosurgical intervention less than 28 days after the last bevacizumab application. The pattern of the bleeding complication (both intracerebral and intraventricular hemorrhage and ecchymoses in the entire course of the tunneled catheter) is highly indicative for a dysfunctional hemostasis. A comparable surgical procedure (implantation of a ventriculo-peritoneal shunt) was performed without complications in another patient from this group who had received bevacizumab on the day of surgery. Since there is no clinical or laboratory test to assess the hemostatic deficit induced by bevacizumab, preoperative estimation of the bleeding risk is not possible. The mechanisms underlying the dysfunctional hemostasis in some patients receving bevacizumab remains elusive. The development of bleeding might result from damage of the vascular integrity since VEGF is considered a survival factor for endothelial cells. Furhtermore bevacizumab might impair the coagulation cascade by inhibiting Tissue Factor expression. The bleeding complication reported here occurred after patient #6 had received a single application of bevacizumab 5 mg/kg making a cumulative toxicity unlikely. Nervertheless, the risk for bleeding or wound healing complications was not excessively high even if the cessation of bevacizumab treatment was less than 28 days prior to the intervention (8 out of 9 patients from the early and emergency surgery group did not have any surgical complications).

A previous report by Clarke et al. on wound healing complications after repeat craniotomy has found a very high rate of impaired healing in 23 patients with preoperative bevacizumab treatment undergoing second (impaired healing in 4 of 14 patients, 29%) or third (impaired healing in 4 of 9 patients, 44%) craniotomy [26]. Our patient cohort comprises 12 patients who underwent second craniotomy and had preoperative bevacizumab therapy within 3 months before surgery. Of these, only one patient (8%) developed a wound healing complication (small wound dehiscence and CSF leakage). The delay from the last bevacizumab application to surgery was considerably longer (42 days) in the 12 patients reported here compared to the 14 second craniotomy patients (30 days) in the series by Clarke

and co-workers. This might play a role in the different rates of wound-healing complications.

Phase II clinical trials on surgical complications in neurosurgical patients receiving bevacizumab postoperatively have reported wound-healing complications in 4-6% [6,14,21]. In the present study, a comparable 5% (1 of 20 patients who received bevacizumab exclusively after the index operation) wound-healing complication rate was found.

In congruence with the published work, we found that postoperative bevacizumab is not associated with a high incidence of surgical complications when therapy is delayed for 4-6 weeks. One patient of 20 (5%) treated with bevacizumab after the index operation developed a wound-healing complication.

CONCLUSION

Our data support the notion that preoperative bevacizumab treatment – especially if the delay between bevacizumab and surgery is short – carries an unpredictable risk for bleeding complications. As there is no clinical or laboratory test to assess the bleeding risk induced by bevacizumab, we recommend confining emergent surgical interventions to the very necessary extent. Bevacizumab therapy should be discontinued 4 weeks prior to elective neurosurgical interventions.

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