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SHORT COMMUNICATION

Bevacizumab induced reversible thrombocytopenia in a patient with recurrent high-grade glioma: a case report

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Abstract We report a case of bevacizumab (BEV)-induced thrombocytopenia in a 36-year-old woman treated with BEV as a single-agent for a recurrent high-grade glioma. The thrombocytopenia was both reversible and reproducible on multiple treatment cycles. The patient has improved clinically and by brain MR imaging with single-agent BEV for approximately 7 months to date. She did not have bleeding or thromboembolic complications. Treatment delays have been 1–2 weeks relative to a conventional plan of treatment, i.e., 10 mg/kg every 2 weeks. This is a rare complication that has not been previously reported.

Keywords Bevacizumab · Glioma · Thrombocytopenia · Complication

Introduction

Recurrent glioblastoma multiforme is rapidly progressive and carries a poor prognosis. Most recently, Cloughesy et al. [1] reported encouraging results with the use of single-agent BEV in this setting with 6-month progression-free survival of 35% and overall survival greater than 9 months. (On 5 May 2009 bevacizumab was granted approval to treat glioblastoma under the US Food and Drug Administration's accelerated approval program.)

We report the case of a 36-year-old woman with recurrent high-grade glioma with multiple prior therapies who has improved clinically and by brain MR imaging with single-agent BEV. She was observed to develop reversible and reproducible BEV-induced thrombocytopenia. It is noteworthy that BEV is most often given in combination with chemotherapy; this is the only indication for single-agent use of BEV. Monitoring for thrombocytopenia may be easily overlooked and practitioners may not consider obtaining regular platelet evaluations. The theoretical basis of this toxicity and its possible implications are discussed.

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Case report

The patient's history dates to 1997 when she was diagnosed with a grade III astrocytoma treated with gross total tumor resection followed by adjuvant radiotherapy.

A recurrence in August of 2003 resulted in a right frontoparietal re-craniotomy for a gross total resection of tumor. Pathology revealed a grade III astrocytoma with a small oligodendrocytic component and a negative 1p/19q deletion. Treatment was initiated with a phase I–II study of CPT-11 and temozolomide (TMZ) on a North American Brain Tumor Consortium Group (NABTC) protocol for recurrent malignant gliomas in October of 2003. The patient received CPT-11 200 mg/m^2 on days 1 and 15 and temozolomide 150 mg/m^2 per day on days 1–5 every 4 weeks for a total of 12 planned cycles, completed in August of 2004.

The patient remained in remission until she presented with left-sided sensory changes, dizziness and gait imbalance, and was found to have recurrence with new areas of edema and abnormal enhancement within the right post central gyrus in February of 2006. She was placed on temozolomide 200 mg/m^2 per day from days 1 through 6 every 4 weeks and progressed in April of 2006.

She started on a NABTC protocol consisting of erlotinib (150 mg daily) and CCI-779 (15 mg given IV weekly) in

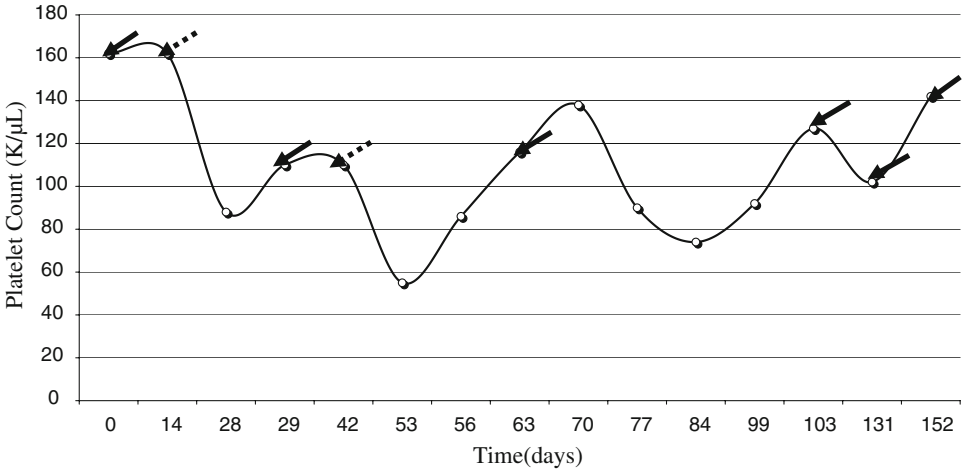

Fig. 1 Platelet count in relationship to treatment with bevacizumab

April of 2006 and progressed after two cycles in June of 2006.

After referral to radiation oncology, she received pulsed, reduced dose rate radiotherapy with a total of 27 daily treatments delivering a dose of 54 Gy, completed in July of 2006 [2].

Disease progression was noted in August of 2007, and dose-intense TMZ was initiated (75 mg/m^2 × 21/28 days). Progression was noted after two cycles in October of 2007.

She was then switched to CCNU at 70 mg/m^2 every 4 weeks, required dose reductions of CCNU due to development of a trend to decreasing platelet counts, at a nadir of 100,000, until her disease progressed in July of 2008.

Tamoxifen (140 mg/day) was started July of 2008; its use was predicated on its activity as a protein kinase C inhibitor [3].

She subsequently presented with new neurological symptoms with left hand weakness and a left foot drop in September of 2008. MRI of the brain demonstrated progression of disease with increased nodular enhancement within the right parietal lobe at and adjacent to the prior surgical site. There was also interval increase in the T2 white matter signal within the right parietal and posterior frontal lobes. She was given high-dose dexamethasone with improvement in the neurological deficits. Based on the fact that she had CPT-11 in the past and recent randomized study suggested BEV had a slightly better survival than BEV/CPT-11 [1], she was started on single-agent BEV at 10 mg/kg every 2 weeks. Parenthetically, despite not having a confirmatory biopsy, we presume the patient's disease converted to a glioblastoma, as would be expected in the natural course of her disease and the fact that she had negative 1p/19q deletion in 2003.

She has tolerated treatment well with some improvement in neurological status as well her brain MRI. She did, however, develop thrombocytopenia with a platelet count of 88,000 after two doses of BEV. Initial workup was unrevealing. She did not have a central venous access and was not receiving heparin. There were no other known medications that could be linked to the development of drug-induced thrombocytopenia. Other hematologic parameters, fibrinogen, fibrin monomer, D-dimer, PT/aPTT, platelet antibodies, peripheral smear, bilirubin, LDH, and haptoglobin were unremarkable on two separate occasions. A repeat platelet count on the same day was 110,000 and the patient received two additional doses of BEV. Her platelet count dropped down to 86,000 after the fourth dose, treatment was held and the platelet count recovered within 3 weeks. Since then, she has been re-challenged and there was once again a clear drop in the platelet count after exposure to BEV with subsequent recovery within approximately 3 weeks (see Fig. 1).

After extensive discussion with the patient and her family members, it was decided to continue treatment with BEV (10 mg/kg) every 3 weeks, as long as platelet counts were above 100,000 and the patient was tolerating treatment.

Discussion

As described, this patient developed thrombocytopenia, attributed to BEV. This is a rare complication that has not been reported in the literature. She is a young woman who has received many prior therapies with resulting decreased bone marrow reserve. She has responded to single-agent BEV with stable disease and clinical improvement.

The exact mechanism of thrombocytopenia is unknown and has not been described to date.

BEV is a humanized immunoglobulin (Ig) G1 monoclonal antibody that binds to and inhibits the activity of vascular endothelial growth factor (VEGF). A meta-analysis by Kut et al. [4] concluded that VEGF in cancer patients is mostly concentrated in the platelets within the blood

compartment and that the cancer itself is not the main source of VEGF in the body.

It has also been shown that platelets take up bevacizumab in vitro and in vivo. In seven cancer patients with solid tumors (five colorectal and two kidney cancer), bevacizumab uptake by platelets was seen after 8 h of administration, resulting in almost complete neutralization of platelet VEGF. It was also shown in rabbits by flow cytometry that platelets containing bevacizumab were cleared from the circulation with a half-life of approximately 48 h, suggesting that there are differences in platelet and plasma bevacizumab pharmacokinetics that may be of clinical relevance [5].

Is bevacizumab causing platelet dysfunction and consumption leading to shortened platelet half-life in this case? It seems that overt thrombocytopenia would then develop once the compensatory mechanisms of the bone marrow became exhausted, particularly in a patient who has had multiple prior therapies.

Another proposed mechanism can be derived by Meyer et al. [6]. They provide evidence that BEV-immune complexes can directly induce platelet aggregation and granule release in vitro and cause thrombocytopenia and thrombosis in vivo in a murine model [6].

Bevacizumab therapy is rapidly expanding into the field of neuro-oncology. One other concern is the development of intra-cranial hemorrhage with thrombocytopenia and BEV therapy. One small retrospective series has suggested that BEV can be used in the setting of venous thromboembolism and anticoagulation, but the safety of BEV has not been established and the risk of intracerebral hemorrhage should be considered [7]. Additionally, it is unclear if thrombocytopenia is associated with thrombosis, in a manner similar to the well-described heparin-induced thrombocytopenia as postulated by Meyer et al. [6].

Our patient has not had thrombotic or bleeding complications to date and continues on therapy.

It is the intention of this report to bring heightened awareness to this potential complication, which may have significant implications for clinical care and ongoing research.

References

1. Cloughesy TF, Prados MD, Wen PY et al (2008) A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab (BV) alone or in combination with irinotecan (CPT) on 6-month progression-free survival in recurrent, treatment-refractory glioblastoma (GBM). J Clin Oncol 26:2010b
2. Cannon GM, Tomé WA, Robins HI et al (2007) Pulsed reduced dose-rate radiotherapy: a novel re-treatment strategy in the management of recurrent glioblastoma multiforme. J Neurooncol 83:307–311
3. Robins HI, Won M, Sieferheld WF et al (2006) A phase II trial of conventional radiation therapy plus high dose tamoxifen for the treatment of supratentorial glioblastoma multiforme: RTOG protocol BR-0021. Neuro Oncol 8:47–52
4. Kut C, Mac Gabhann F, Popel AS (2007) Where is VEGF in the body? A meta-analysis of VEGF distribution in cancer. Br J Cancer 97:978–985
5. Verheul H, Lolkema M, Qian D et al (2007) Platelets take up the monoclonal antibody bevacizumab. Clin Can Res 13:5341–5347
6. Meyer T, Robles-Carrilo L, Robson T et al (2009) Bevacizumab immune complexes activate platelets and induce thrombosis in FCGR2A transgenic mice. J Thromb Haemost 7:171–181
7. Nghiemphu PL, Green RM, Pope WB et al (2008) Safety of anticoagulation use and bevacizumab in patients with glioma. Neuro Oncol 10:355–360