Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment

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Received 9 June 2011 and in revised form 9 July 2011

Summary

Background: Posterior reversible encephalopathy syndrome (PRES) is a potentially devastating complication of bevacizumab treatment.

Aim: We examined the clinical features, treatment and outcomes of patients who developed PRES following bevacizumab treatment at our institution and those reported in the literature.

Design: Retrospective audit and systematic review.

Methods: Patients were identified from the Mayo Clinic database and the published literature using ‘PubMed’ and ‘OVID’ databases, from January 2006 to June 2010, who developed PRES features within 3 weeks of bevacizumab treatment, who had brain imaging findings of focal vasogenic edema and radiologic proof of reversibility.

Results: Two patients with definite PRES were identified from our institution and a further 10 cases were identified from the published literature (total, n = 12). The mean age of these patients was 52 years (range 4–68 years), four of whom were men and eight women. Headaches (n = 7), seizures (n = 6), visual disturbances (n = 5) and nausea and vomiting (n = 3) were the common presenting symptoms. In a majority of patients (n = 10), an increase in blood pressure from their baseline values was observed during their acute presentation. PRES resolved following withdrawal of bevacizumab and blood pressure control in all patients.

Conclusions: PRES is a catastrophic neurological complication of bevacizumab treatment, which responds favorably to prompt bevacizumab withdrawal and blood pressure control.

Introduction

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a distinct clinicoradiological entity characterized by a constellation of clinical features (such as headaches, seizures, encephalopathy and visual disturbances) and focal reversible vasogenic edema involving predominantly the parietal and occipital lobes.1 PRES has been described in association with severe hypertension, pre-eclampsia or eclampsia, cerebrovascular events, renal disease, sepsis, autoimmune conditions, organ transplantation and, less frequently, following the administration of immunosuppressive agents and cytotoxic drugs.2,3 Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA), a recombinant humanized monoclonal anti-
vascular endothelial growth factor (VEGF) antibody, is the first biologic agent clinically proven to extend survival in malignant diseases and is approved in the USA as a first-line treatment for metastatic carcinoma of the colon and rectum.4,5

The association between bevacizumab and PRES was first highlighted in 2006, following the development of encephalopathy and reversible vasogenic edema on brain imaging in two patients as part of treatment for metastatic renal and rectal carcinoma.6,7 With wider clinical experience, numerous reports that linked the development of PRES to the use of bevacizumab have emerged.8–15 We examined the clinical features, treatment and outcomes of patients who developed PRES following bevacizumab treatment at our institution and those reported in the literature.

Methods

Patients were identified from the electronic database at the Mayo Clinic, Rochester, MN, using a text-retrieval system and searching for patients who received ‘bevacizumab’ or ‘Avastin’, and in whom the terms ‘reversible encephalopathy’, ‘PRES’ or ‘RPLS’ were described within their clinical notes from January 2006 to June 2010. The presence of all three of the following criteria was mandated for study inclusion: (i) clinical history of acute neurologic change including headache, encephalopathy, seizure, visual disturbance or focal deficits; (ii) brain imaging findings of focal vasogenic edema; and (iii) radiologic proof of reversibility.16 Patient records were assessed for demographic information, indications for the administration of bevacizumab, clinical summary and blood pressure measurements, medications administered with bevacizumab, location of brain lesions, management and clinico-radiological outcomes. We identified previously reported cases of PRES following the use of bevacizumab by reviewing the ‘PubMed’ and ‘OVID’ databases using the terms ‘bevacizumab’ or ‘Avastin’, ‘reversible encephalopathy’, ‘PRES’ and ‘RPLS’. The study was approved by the Mayo Clinic Institutional Review Board.

Results

From a list of 10 381 patients who received ‘bevacizumab’ and ‘Avastin’ at our institution during the study period, we identified 8 patients in whom either terms ‘reversible encephalopathy’, ‘PRES’ or ‘RPLS’ was described in their medical records. Five patients were suspected to have PRES on the basis of their clinical presentations but without radiological confirmation: one probable case had clinical and radiological features of PRES but no proven reversibility on follow-up imaging, and two definite cases had clinical and radiological features of PRES with evidence of resolution of the vasogenic edema on repeat brain magnetic resonance imaging (MRI). The case histories of these definite cases of PRES are described in greater detail below.

Patient 1

A 68-year-old female, diagnosed with metastatic nonsmall cell lung carcinoma, developed severe headaches and acute confusion 14 days following her third dose of bevacizumab that was administered in combination with paclitaxel and carboplatin. Her headaches were described as constant, localized over the vertex of her head and they were associated with nausea and vomiting. She was also noted to be increasingly confused over 2 days by her husband. Her medical comorbidities included hypertension and hyperlipidemia. Neurologic examination revealed neck rigidity and nominal aphasia, but was otherwise normal. Apart from elevated blood pressure of 221/84 mmHg, her cardiac, respiratory and abdominal examinations were within normal limits. Brain MRI showed areas of hyperintense T2-weighted signal and increased apparent diffusion coefficient (ADC) in both cerebellar hemispheres; these regions enhanced with gadolinium on T1-weighted imaging (Figure 1). The patient had a normal brain MRI performed <2 months earlier. Cerebrospinal fluid (CSF) was clear, colorless and acellular. Electroencephalogram did not reveal epileptiform activity. Following discontinuation of chemotherapeutic medications and control of the hypertension with intravenous labetalol, her neurological complaints improved the following day. Brain MRI repeated 8 days later showed complete reversibility of the abnormal changes. Bevacizumab was not reinitiated and she tolerated the remaining cycles of chemotherapy without recurrence of PRES.

Patient 2

A 63-year-old hypertensive female developed generalized seizures and visual disturbances 8 days following administration of bevacizumab in combination with gemcitabine and oxaliplatin for treatment of pancreatic carcinoma. Neurological examination was significant for cortical blindness. Blood pressure was recorded at 190/94 mmHg and the remaining cardiovascular, respiratory and abdominal assessments were within normal limits. Brain MRI showed patchy T2-hyperintense and T1-hypointense lesions in the subcortical white
matter of bilateral parieto-occipital regions with elevated ADC values. Gadolinium was not administered in this patient. CSF was clear, colorless and acellular, and electroencephalogram did not reveal epileptiform discharges. Her neurologic symptoms resolved fully 1 day later, and a repeat brain MRI 1 month later confirmed the resolution of the vasogenic edema. Bevacizumab was discontinued and she tolerated the remaining cycles of chemotherapy without recurrence of PRES.

**Review of previously reported cases**

To date, a total of 12 cases of PRES following the administration of bevacizumab have been reported in the literature (Table 1).6–15 The mean age at presentation of these patients was 52 years (range 4–68 years), four of whom were men and eight women. Headaches ($n=7$), seizures ($n=6$), visual disturbances ($n=5$) and nausea and vomiting ($n=3$) were the common presenting symptoms. In a majority of patients, an increase in blood pressure from their baseline values was observed during their hospitalization. PRES occurred in two patients who received bevacizumab as monotherapy6,14 and the rest had received bevacizumab in combination with other chemotherapeutic agents (oxaliplatin, $n=5$; fluorouracil, $n=4$; leucovorin, $n=3$; gemcitabine, $n=2$; doxorubicin, $n=1$; carboplatin, $n=1$; capecitabine, $n=1$; and irinotecan, $n=1$). In all these patients, PRES resolved following withdrawal of bevacizumab and strict control of blood pressure. Two patients also received prednisolone and mannitol as part of their treatment for PRES.9,14

![Figure 1. Brain MRI showed hyperintensities on fluid attenuation inversion recovery (FLAIR) images in both cerebellar hemispheres which enhanced with gadolinium on T1-weighted imaging.](https://academic.oup.com/qjmed/article-abstract/105/1/69/1559457)

**Discussion**

Although generally well tolerated, the use of bevacizumab has been associated with severe adverse effects such as gastrointestinal tract perforation, wound dehiscence, hemorrhage, arterial thromboembolic events, hypertensive crisis, cerebrovascular events, nephrotic syndrome and congestive heart failure.16,17 In this study, we identified two definite cases of PRES following the administration of bevacizumab to treat advanced malignancies. The diagnosis of PRES was supported by characteristic clinical and radiologic features that resolved following cessation of bevacizumab and blood pressure control. Bevacizumab was implicated as the most likely offending agent given that the subsequent re-introduction of the other chemotherapy agents did not result in recurrent PRES. In a review of previously reported cases (Table 1), the association between PRES and bevacizumab used as a single agent was reported in two patients,6,14 while the remaining cases were observed in association with other chemotherapy agents,7–13,15 the most common combination comprising oxaliplatin and 5-fluorouracil. In patient 1, gadolinium enhancement was observed on brain MRI 1 day after the onset of symptoms, a radiological feature that has been reported in a minority of PRES cases.1,16

VEGF is a naturally occurring, endothelial, cell-specific glycoprotein that regulates angiogenesis and contributes to the pathogenesis of proliferative retinopathy, age-related macular degeneration and tumor-related neovascularization.9 In vivo topical administration of VEGF results in an increase in
Table 1  Comparison of previously reported cases of PRES associated with bevacizumab treatment

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<th>Authors</th>
<th>Demographics and indications for bevacizumab use</th>
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<th>Medications administered</th>
<th>Radiologic findings</th>
<th>Management</th>
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<tr>
<td>Glusker et al.</td>
<td>6 59-year-old woman Metastatic renal cancer</td>
<td>Seizures, cortical blindness and extensor plantar responses BP 168/88 mmHg (baseline 100/70 mmHg)</td>
<td>Intravenous bevacizumab alone</td>
<td>Frontal and parieto-occipital subcortical lesions on MRI brain</td>
<td>No antihypertensive administered</td>
<td>Neurologic deficits recovered 4 days later MRI changes resolved 6 weeks later</td>
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<td>Ozcan et al.</td>
<td>7 52-year-old woman Metastatic rectal adenocarcinoma</td>
<td>Headaches, confusion and cortical blindness BP 172/100 mmHg (baseline not mentioned)</td>
<td>Intravenous bevacizumab in combination with fluorouracil, leucovorin and oxaliplatin</td>
<td>Occipital subcortical lesions on MRI brain</td>
<td>Antihypertensive medications (details not mentioned)</td>
<td>Neurologic recovery 3 days later Radiologic resolution not mentioned</td>
</tr>
<tr>
<td>Allen et al.</td>
<td>8 52-year-old man Metastatic rectal carcinoma</td>
<td>Headaches, bilateral cortical blindness and seizures Systolic BP range, 140–150 mmHg (baseline not mentioned)</td>
<td>Intravenous bevacizumab in combination with irinotecan, leucovorin and 5-fluorouracil (as part of the FOLFIRI regimen)</td>
<td>Parieto-occipital subcortical lesions on MRI brain</td>
<td>Antihypertensive medications (details not mentioned)</td>
<td>Neurologic deficits recovered 10 days later MRI brain improved 4 days later</td>
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<td>Burki et al.</td>
<td>9 33-year-old woman Metastatic breast cancer</td>
<td>Headaches, gastric pain, nausea and vomiting BP 150/100 mmHg (baseline 100/70 mmHg)</td>
<td>Intravenous bevacizumab in combination with doxorubicin</td>
<td>Frontal and parieto-occipital subcortical lesions on MRI brain</td>
<td>Prednisolone, furosemide, nicardipine and mannitol</td>
<td>Neurologic and MRI changes resolved 1 day later</td>
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<td>Maalouf et al.</td>
<td>10 55-year-old woman Metastatic colon cancer</td>
<td>Lethargy, dysarthria and generalized seizures BP 190/120 mmHg (baseline reported normal)</td>
<td>Intravenous bevacizumab in combination with fluorouracil and leucovorin</td>
<td>Pontomedullary lesions on MRI brain</td>
<td>Oral amlodipine</td>
<td>Neurologic deficits resolved 1 day later MRI changes resolved 21 days later</td>
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<td>Levy et al.</td>
<td>11 4-year-old man Hepatoblastoma</td>
<td>Severe headache and seizures BP 160/120 mmHg (baseline 106/60 mmHg)</td>
<td>Intravenous bevacizumab in combination with gemcitabine and oxaliplatin</td>
<td>Frontal and parieto-occipital subcortical lesions on MRI brain</td>
<td>Anti-hypertensive medications (details not mentioned)</td>
<td>Neurologic deficits resolved 13 days later MRI changes resolved 21 days later</td>
</tr>
<tr>
<td>Koopman et al.</td>
<td>12 49-year-old man Colorectal cancer</td>
<td>Unconsciousness, seizures and urinary incontinence BP 180/100 mmHg (baseline 150/90 mmHg)</td>
<td>Intravenous bevacizumab in combination with oxaliplatin and capecitabine</td>
<td>Occipital lesions on CT brain</td>
<td>Anti-hypertensive medications (details not mentioned)</td>
<td>Neurologic deficits resolved 2 days later CT brain changes resolved 6 weeks later</td>
</tr>
</tbody>
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(continued)
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<th>Authors</th>
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<tr>
<td>Peter et al.</td>
<td>57-year-old woman Metastatic colon carcinoma</td>
<td>Cortical blindness BP 140/70 mmHg (baseline not mentioned)</td>
<td>Intravenous bevacizumab in combination with 5-fluorouracil, oxaliplatin and leucovorin (as part of the FOLFOX regimen)</td>
<td>Parieto-occipital subcortical lesions on MRI brain</td>
<td>No anti-hypertensive administered</td>
<td>Neurologic deficits recovered 4 weeks later MRI brain resolved 7 weeks later.</td>
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<td>Artunay et al.</td>
<td>67-year-old man Age-related macular degeneration</td>
<td>Headaches, lethargy, nausea and vomiting BP 170/110 mmHg (baseline, 120/75 mmHg)</td>
<td>Intravitreal bevacizumab alone</td>
<td>Parieto-occipital subcortical lesions on MRI brain</td>
<td>Prednisolone, nicardipine and mannitol</td>
<td>Neurologic deficits improved one day later MRI changes resolved 2 days later Neurologic recovery within a week</td>
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<tr>
<td>Lau et al.</td>
<td>63-year-old woman Metastatic rectosigmoid carcinoma</td>
<td>Headaches, drowsiness and visual disturbance BP not mentioned</td>
<td>Intravenous bevacizumab in combination with oxaliplatin and 5-fluorouracil</td>
<td>Posteriorinferior parietotemporal subcortical lesions on MRI brain</td>
<td>Supportive measures (details not mentioned)</td>
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<td>Present study</td>
<td>68-year-old woman Metastatic nonsmall cell lung carcinoma</td>
<td>Headaches, confusion, nausea and vomiting BP 221/84 mmHg (baseline 130/84 mmHg)</td>
<td>Intravenous bevacizumab in combination with taxol and carboplatin</td>
<td>Cerebellar lesions on MRI brain</td>
<td>Oral anti-hypertensive medications</td>
<td>Neurologic recovery one day later MRI changes resolved 8 days later Neurologic recovery 4 days later MRI changes resolved 30 days later</td>
</tr>
<tr>
<td></td>
<td>63-year-old woman Advanced pancreatic carcinoma</td>
<td>Seizures and cortical blindness BP 190/94 mmHg (baseline 120/82 mmHg)</td>
<td>Intravenous bevacizumab in combination with gemcitabine and oxaliplatin</td>
<td>Parieto-occipital lesions on MRI brain</td>
<td>Oral anti-hypertensive medications</td>
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BP: blood pressure.
fenestration in the endothelium of small venules and capillaries, thus facilitating its vasodilatory effects, a process thought to be mediated by nitric oxide and prostacyclin production. In contrast, inhibition of VEGF function disrupts angiogenesis in brain tumors and causes vasoconstriction. Clinical studies indicate that inhibition of VEGF may result in systemic hypertension, as Grade 3 or 4 hypertension has been reported in 5–18% of patients treated with bevacizumab. Severe hypertension has been observed in up to 70–80% of PRES patients, although the role of hypertension and changes in cerebral perfusion in the pathogenesis of PRES remains a matter of debate. Similarly, in this review, we found that the majority of patients had elevated blood pressure during their acute hospitalization for PRES. Although acute hypertension was more common in patients with PRES, one study found that fluctuations in blood pressure were not more common in PRES cases compared with controls matched for age and history of hypertension. We hypothesize that an increase in blood pressure in a ‘locus minoris resistentiae’ added to the changes in endothelial function induced by bevacizumab, thus contributing to the occurrence of PRES.

Prompt withdrawal of bevacizumab and blood pressure control were followed by very rapid resolution of symptoms in our patients. Resolution of MRI abnormalities was observed in as early as 1 day after the onset of PRES symptoms (Table 1), consistent with findings that showed the effects of bevacizumab on capillary density to be readily and rapidly reversible. PRES does not appear to be a complication unique to the use of bevacizumab. Several studies report PRES following administration of other anti-angiogenic agents (e.g. sunitinib) and anti-tumor necrosis factor-α inhibitors (e.g. infliximab).

Our study has several limitations. First, data on cerebral perfusion and PRES, which may be useful to elucidate the pathophysiological link between bevacizumab, acute hypertension and PRES, were not available in our patients. Second, we included only reported cases in the English literature and may have inadvertently excluded cases that were either reported in other languages. Third, the contribution of other chemotherapy agents to the development of PRES cannot be ruled out since the majority of reported patients had received bevacizumab in combination with other cytotoxic agents. It remains possible that the bevacizumab alone might not cause PRES and that PRES occurs more frequently when bevacizumab is combined with other agents. To date, PRES has been reported in only one patient following administration of bevacizumab through the intravitreal route for age-related macular degeneration. A high level of suspicion for PRES is advisable in patients who develop headache, confusion or visual disturbances during bevacizumab treatment, either as monotherapy or in combination with other chemotherapeutic agents. These data support the need for close vigilance of neurological features and blood pressure monitoring of patients undergoing bevacizumab treatment. Prompt withdrawal of bevacizumab and blood pressure control appear to portend favorable outcomes in these patients.

Conflict of interest: None declared.

References


